```
$%^Dialog;HighlightOn=%%%;HighlightOff=%%%;
? b 411;set files biotech
     22may08 13:07:35 User219511 Session D727.2
        $0.00   0.115 DialUnits File410
    $0.00 Estimated cost File410
    $0.22 TELNET
    $0.22 Estimated cost this search
    $0.76 Estimated total session cost   0.265 DialUnits
File 411:DIALINDEX(R)

DIALINDEX(R)
  (c) 2008 Dialog

*** DIALINDEX search results display in an abbreviated ***
*** format unless you enter the SET DETAIL ON command. ***
  You have 25 files in your file list.
  (To see banners, use SHOW FILES command)
? s (chordin or noggin or DAN or veinless) and stent?

Your SELECT statement is:
  s (chordin or noggin or DAN or veinless) and stent?

      Items   File
      -----   ----
          1     5: Biosis Previews(R)_1926-2008/May W3
          3    34: SciSearch(R) Cited Ref Sci_1990-2008/May W4
          4    73: EMBASE_1974-2008/May 21
         13   135: NewsRx Weekly Reports_1995-2008/May W3
          4   144: Pascal_1973-2008/May W3
          4   155: MEDLINE(R)_1950-2008/May 21
          1   266: FEDRIP_2008/Feb
          1   357: Derwent Biotech Res.__1982-2008/Apr W3
          1   370: Science_1996-1999/Jul W3
          2   399: CA SEARCH(R)_1967-2008/UD=14821

  10 files have one or more items; file list includes 25 files.

? save temp; b 155,5,34,73,135,144,266,357,370,399;exs;rd
Temp SearchSave "TH560436835" stored
     22may08 13:08:28 User219511 Session D727.3
        $1.86   0.633 DialUnits File411
    $1.86 Estimated cost File411
    $0.26 TELNET
    $2.12 Estimated cost this search
    $2.88 Estimated total session cost   0.897 DialUnits

SYSTEM:OS - DIALOG OneSearch
  File 155:MEDLINE(R) 1950-2008/May 21
       (c) format only 2008 Dialog
*File 155: MEDLINE has reloaded. Please see HELP NEWS 155
for details.
  File   5:Biosis Previews(R) 1926-2008/May W3
       (c) 2008 The Thomson Corporation
  File  34:SciSearch(R) Cited Ref Sci 1990-2008/May W4
       (c) 2008 The Thomson Corp
  File  73:EMBASE 1974-2008/May 21
       (c) 2008 Elsevier B.V.
*File  73: The 2008 EMTREE Thesaurus has been loaded. Please see
HELP NEWS 72 for details.
  File 135:NewsRx Weekly Reports 1995-2008/May W3
       (c) 2008 NewsRx
  File 144:Pascal 1973-2008/May W3
       (c) 2008 INIST/CNRS
  File 266:FEDRIP 2008/Feb
       Comp & dist by NTIS, Intl Copyright All Rights Res
  File 357:Derwent Biotech Res. _1982-2008/Apr W3
       (c) 2008 The Thomson Corp.
  File 370:Science 1996-1999/Jul W3
       (c) 1999 AAAS
*File 370. This file is closed (no updates). Use File 47 for more current
information.
  File 399:CA SEARCH(R) 1967-2008/UD=14821
       (c) 2008 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
IPCR/8 classification codes now searchable as IC=. See HELP NEWSIPCR.

    Set  Items  Description
    ---  -----  -----------
Executing TH560436835
        2173  CHORDIN
        4763  NOGGIN
        8721  DAN
          92  VEINLESS
      191681  STENT?
    S1    34  (CHORDIN OR NOGGIN OR DAN OR VEINLESS) AND STENT?
    S2    30  RD  (unique items)
? ts2/7/1-30

 2/7/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

16756342  PMID: 16385833
  [Palliative treatment of esophageal cancer with dysphagia: more
favourable outcome from single-dose internal brachytherapy than from the
placement of a self-expanding %%%stent%%%, a multicenter randomised study]
  Palliatieve behandeling voor slokdarmkanker met passageklachten:
gunstiger uitkomsten van eenmalige inwendige brachytherapie %%%dan%%% van
plaatsing van een zelfexpanderende %%%stent%%% ; multicentrisch,
gerandomiseerd onderzoek.
  Homs M Y V; Steyerberg E W; Eijkenboom W M H; Tilanus H W; Stalpers L J A
; Bartelsman J F W M; van Lanschot J J B; Wijrdeman H K; Mulder C J J;
Reinders J G; Boot H; Aleman B M P; Kuipers E J; Siersema P D
  Afd. Maag-, Darm- en Leverziekten, Erasmus MC, locatie Dijkzigt, Postbus
2040, 3000 CA Rotterdam.
  Nederlands tijdschrift voor geneeskunde (Netherlands)  Dec 10 2005,  149
(50) p2800-6.  ISSN 0028-2162--Print  Journal Code: 0400770
  Publishing Model:Print; Comment in Ned Tijdschr Geneeskd. 2005 Dec
10;149(50):2775-82; Comment in PMID 16385829
  Document type: Comparative Study; Duplicate Publication; English Abstract
; Journal Article; Multicenter Study; Randomized Controlled Trial, Research
Support, Non-U.S. Gov't
  Languages: DUTCH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed
  OBJECTIVE: To compare the results of single-dose internal irradiation
(brachytherapy) and self-expanding metal %%%stent%%% placement in the
palliation of oesophageal obstruction due to cancer of the oesophagus.
DESIGN: Randomised trial. METHOD: In the period from December 1999-Jun
2002, 209 patients with dysphagia due to inoperable carcinoma of the
oesophagus were randomised to placement of an Ultraflex %%%stent%%% (n =
108) or single-dose (12 Gy) brachytherapy (n = 101). Primary outcome was
relief of dysphagia; secondary outcomes were complications, persistent or
recurrent dysphagia, health-related quality of life, and costs. Patients
were followed up by monthly home visits from a specialised nurse. RESULTS:
Dysphagia improved more rapidly after %%%stent%%% placement than after
brachytherapy, but long-term relief of dysphagia was better after
brachytherapy. %%%Stent%%% placement resulted in more complications than
did brachytherapy (36/108 (33%) versus 21/101 (21%); p = 0.02), due mainly
to an increased incidence of late haemorrhage in the %%%stent%%% group (14
versus 5; p = 0.05). The groups did not differ with regard to the incidence
of persistent or recurrent dysphagia or median survival (p > 0.20). In the
long term, quality-of-life scores were higher in the brachytherapy group.
Total medical costs were also similar for both treatments: Euro 8,215 for
%%%stent%%% placement and Euro 8,135 for brachytherapy. CONCLUSION:
Brachytherapy provided better long-term relief of dysphagia than did
%%%stent%%% placement and also produced fewer complications. Brachytherapy
is therefore recommended as the preferred treatment for the palliation of
dysphagia due to oesophageal cancer.
  Record Date Created: 20060102
```

Record Date Completed: 20060216

2/7/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

14759639 PMID: 12184083
Interstitial laser coagulation and biodegradable self-expandable, self-reinforced poly-L-lactic and poly-L-glycolic copolymer spiral %%%stent%%% in the treatment of benign prostatic enlargement.
Laakkovirta Susanna; Isotalo Taina; Talja Martti; Valimaa Tero; Tormala Pertti; Tammela Teuvo L J
Department of Urology, Tampere University Hospital, Medical School, University of Tampere, Tampere, Finland.
Journal of endourology / Endourological Society (United States) Jun 2002, 16 (5) p311-5, ISSN 0892-7790--Print Journal Code: 8807503
Publishing Model Print
Document type: Clinical Trial; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND AND PURPOSE: Interstitial laser coagulation of the prostate (ILCP) induces necrosis, edema, and an increased risk of postoperative urinary retention. The object here was to evaluate the efficacy, safety, and utility of a new self-expandable self-reinforced (SR) PLGA copolymer(lactic:glycolic ratio 80/20) spiral %%%stent%%% inserted after ILCP to promote voiding. The SR-PLGA %%%stent%%% has a degradation time of 2 to 2.5 months. PATIENTS AND METHODS: Fifty men with a mean age of 70.5 years (range 52-85 years), suffering from lower urinary tract symptoms secondary to benign prostatic enlargement underwent ILCP. A suprapubic catheter was inserted, ILCP performed, and an SR-PLGA 80/20 spiral %%%stent%%% inserted on completion of the operation. The suprapubic catheter was removed when voiding commenced. As prophylactic antibiotic, ciprofloxacin was used in a single dose before ILCP, followed by trimethoprim or nitrofurantoin for 2 weeks. RESULTS: All except three patients started to void on the first postoperative day. In two of the three cases, the %%%stent%%% had moved proximally and had to be relocated, whereafter voiding succeeded. The mean maximum and average flow rates increased, while %%%DAN%%%-PSS-1 symptom score and post voiding residual urine volume decreased statistically significantly. At 2 months, the %%%stent%%% was still intact in the urethra in all except three patients. At 4 months, it had been degraded into small fragments, and at 6 months, it had been completely eliminated. The only exceptions were three patients with an uncalcified piece of the %%%stent%%% in the bladder. Half of the patients had irritative symptoms caused at least partly by ILCP itself: 10% had asymptomatic urinary infection postoperatively. CONCLUSIONS: The self-expandable SR-PLGA copolymer %%%stent%%% is safe and highly biocompatible. It ensures voiding in the case of temporary obstruction caused by prostatic edema. The degradation time is long enough in all patients to cover the need for postprocedure urinary drainage.
Record Date Created: 20020819
Record Date Completed: 20030129

2/7/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

12698066 PMID: 9623158
[Sealing esophagobronchial fistulae. better results with self expanding %%%stents%%% than with an esophagobronchial fistula]
Afsluiting van oesofagobronchiale fistels: betere resultaten met zelfexpanderende %%%stents%%% %%%dan%%% met plastic endoprothesen.
Kooijman W, Taal B G, Boot H
Nederlands Kanker Instituut/Antoni van Leeuwenhoek Ziekenhuis, afd. Gastro-enterologie en Medische Oncologie, Amsterdam.
Nederlands tijdschrift voor geneeskunde (NETHERLANDS) Apr 11 1998, 142 (15) p845-50, ISSN 0028-2162--Print Journal Code: 0400770
Publishing Model Print
Document type: Comparative Study; English Abstract; Journal Article
Languages: DUTCH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: To compare the results of plastic endoprostheses and of self expanding %%%stents%%% in patients with an esophagobronchial fistula. DESIGN: Retrospective, descriptive. SETTING: Nederlands Kanker Instituut/Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, the Netherlands. METHOD: Forty-two patients with an esophagobronchial fistula caused by a malignant tumour in the oesophagus, lungs or mediastinum were fitted with an endoprosthesis during the period 1 January 1991-31 August 1995. Use was made initially of a plastic endoprosthesis with a special tulip funnel (n = 24), later of a coated self expanding %%%stent%%% (n = 18). In seven patients, the fistula had been the first manifestation of the tumour; in 35, a recurrence after earlier treatment was involved. The initial characteristics (sex, age, diagnosis, earlier therapy, signs and symptoms) were the same in both groups. RESULTS: Dilatation immediately before insertion of a plastic endoprosthesis was necessary in 23 patients (96%); such dilatation was necessary in four of the patients (22%) fitted with a self expanding %%%stent%%%. Complete sealing of the fistula was achieved in 19 (79%) and 15 (83%) patients, respectively. Reoperations were necessary in eight (33%) and three (17%) patients. Early major complications occurred in four (17%) and two (11%) patients. CONCLUSION: The selfexpanding %%%stent%%% was faster and easier to insert than a plastic endoprosthesis, and effective in sealing an oesophagobronchial fistula.
Record Date Created: 19981029
Record Date Completed: 19981029

2/7/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

12544888 PMID: 9876701
Therapeutic endoscopy of the hepatobiliary and pancreatic system: a Vietnamese experience.
Anh L Q
Binh Dan Hospital, Department of Digestive Surgery, Ho Chi Minh City, Viet Nam.
JSLS - Journal of the Society of Laparoendoscopic Surgeons / Society of Laparoendoscopic Surgeons (UNITED STATES) Oct-Dec 1997, 1 (4) p345-8, ISSN 1086-8089--Print Journal Code: 100884618
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
INTRODUCTION: Therapeutic endoscopic retrograde cholangiopancreatography (ERCP) was initially utilized at Binh %%%Dan%%% Hospital, Viet Nam, in August 1993. From August 1993 through March 1997, 318 ERCP procedures were performed on 271 patients. It was not possible to obtain cholangiography in 32 cases of the 318 procedures of ERCP, for a success rate of diagnostic ERCP approaching 89%. MATERIALS AND METHODS: Cases treated by ERCP included: 14 cases of Ascaris lumbricoides in the common bile duct (CBD). 69 cases of bile duct stones. 12 cases managed by nasobiliary catheter drainage. 3 cases treated by bile duct %%%stent%%%. Sphincterotomy was attempted on 108 cases. Complications included: 5 cases of acute pancreatitis. 7 cases of purulent cholangitis, which resulted in 1 death. 2 cases of retroperitoneal duodenal perforation. 9 cases of postsphincterotomy bleeding. CONCLUSIONS: We conclude that ERCP is a useful therapeutic modality for bile duct stones and parasitic worms in the bile ducts.
Record Date Created: 19990212
Record Date Completed: 19990212

2/7/5 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2008 The Thomson Corp. All rts. reserv.

08374581 Genine Article#: 277ZZ Number of References: 43
Title: Hemopoietic stem-cell harvesting and transplantation using G-CSF-primed BM: comparison with unprimed BM and G-CSF-primed PBSC
Author(s): Lowenthal RM (REPRINT) ; Tuck D; Tegg E; Marsden KA; Rees B; Luck J; Ragg S; Parker N; Kotlovsky N
Corporate Source: ROYAL HOBART HOSP,HAEMATOL ONCOL UNIT, GPO BOX 1061L/HOBART/TAS 7001/AUSTRALIA/ (REPRINT); ROYAL HOBART HOSP,CLIN HAEMATOL & MED ONCOL UNIT/HOBART/TAS/AUSTRALIA/
Journal: CYTOTHERAPY, 1999, V1, N5, P409-416
ISSN: 1465-3249 Publication date: 19990000
Publisher: ISIS MEDICAL MEDIA LTD, 59 ST ALDATES, OXFORD OX1 1ST, ENGLAND
Language: English Document Type: ARTICLE
Abstract: Background PBSC collected following G-CSF priming lend to more rapid hemopoietic reconstitution (HR) after autologous transplantation than do unprimed BM stem cells. However, PBSC have a number of disadvantages compared with Bill cells, including the need for an extended collection period and requirement for good venous access.

Methods We retrospectively analysed our experience with nit alternative source of hemopoietic %%%xtent%%% cells, G-CSF-printed BM. Forty four patients who underwent BM harvesting after 6 days administration of G-CSF, at a dose of 5 mu g/kg per %%%dan%%%; were compared with an equal number who underwent standard (unprimed) Bill harvesting. We also analysed HR after autologous transplantation in 16 patients who received unprimed BM, 18 who received G-CSF-primed BM and 14 who received PBSC.

Results G-CSF-primed Bill was collected more quickly (p<0.00005) and yielded a larger number of cells (p<0.0001) than unprimed Bill. Consequently: larger numbers of cells were available for administration following transplantation with G-CSF-primed BM. The results of HR after transplantation with G-CSF-primed BM were intermediate between those of unprimed BM and PSBC. and PBSC. For example, platelet independence (unsupported platelet count greater than or equal to 20 x 10(9)/L) occurred after 22 days with unprimed BM 14 days with G-CSF-primed BM and 10 days with PBSC (p for trend <0.0001) and the mean number of days when platelet transfusions were given was 10, 6 and ? respectively (p for trend <0.005). These results reflect ed transplant cell doses.

Conclusion G-CSF-primed BM is a valuable source of hemopoietic stem cells for autologous transplantation and a useful alternative to PBSC in certain circumstances.

2/7/6 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2008 The Thomson Corp. All rts. reserv.

06176963 Genuine Article#: XZ940 Number of References: 24
Title: Two closely-related left-right asymmetrically expressed genes, lefty-1 and lefty-2: their distinct expression domains, chromosomal linkage and direct neuralizing activity in Xenopus embryos
Author(s): Meno C; Ito Y; Saijoh Y; Matsuda Y; Tashiro K; Kuhara S; Hamada H
Corporate Source: OSAKA UNIV,INST MOL & CELLULAR BIOL/SUITA/OSAKA 565/JAPAN/; KYUSHU UNIV,GRAD SCH GENET RESOURCES TECH, HIGASHI KU/FUKUOKA 812/JAPAN/; NATL INST RADIOL SCI,GENOME RES GRP/INAGE/CHIBA/JAPAN/
Journal: GENES TO CELLS, 1997, V2, N8 (AUG), P513-524
ISSN: 1356-9597 Publication date: 19970800
Publisher: BLACKWELL SCIENCE LTD, OSNEY MEAD, OXFORD, OXON, ENGLAND OX2 0E
Language: English Document Type: ARTICLE
Abstract: Background: Vertebrates have numerous lateral asymmetries in the position of their organs, but the molecular basis for the determination of left-right (L-R) asymmetries remains largely unknown. TGF beta-related genes such as lefty and nodal are L-R asymmetrically expressed in developing mouse embryos, and may be involved in GR determination.
Results: We have identified two highly conserved genes, lefty-1 and lefty-2, in the mouse genome. These two genes are tightly linked on mouse chromosome 1. lefty-1 and lefty-2 are both expressed in a L-R asymmetric fashion in mouse embryos. However, the major expression domains of the two genes are different: lefty-1 expression is predominantly confied to the left side of ventral neural tube, whereas lefty-2 is strongly expressed in the lateral plate mesoderm on the left side. In embryos homozygous for the iv and inv mutation, which cause situs inversus, the expression sites of both genes are affected, either reversed or bilaterally, indicating that lefty-1 and lefty-2 are downstream of iv and inv. Although Lefty-1 and Lefty-2 prepro-proteins are not readily processed in cultured cells, BMP2-Lefty chimeric proteins can be processed to a secreted form. We have examined the activities of Lefty-1 and Lefty-2 in Xenopus embryos. In animal cap explants, Lefty-1 and Lefty-2 induce neural cells in the absence of mesoderm induction. The direct neuralizing activities of Lefty-1 and Lefty-2 thus seem remarkably similar to those of BMP antagonists such as %%%noggin%%% and %%%chordin%%%, suggesting that the action of Lefty-1 and Lefty-2 may be to locally antagonize BMP (bone morphogenic protein)mediated signals in tissues positioned on the left side of the mouse embryos.
Conclusion: There are two lefty genes in mice (lefty-1 and lefty-2), both of which are expressed in a LR asymmetric fashion and are downstream of iv and inv. Lefty-1 and Lefty-2 possess direct neuralizing activity in Xenopus embryos, resembling the activities of BMP antagonists.

2/7/7 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0080968950 EMBASE No: 2006028899
Bone morphogenetic protein 4: Potential regulator of shear stress-induced graft neointimal atrophy
Hsieh P.C.H. // Hsieh P.C.H.; Kenagy R.D.; Chang C.M.C.; Justice S.; Clowes A.W. // Mulvihill E.R.; Wang X.; Hudkins K.L.; Alpers C.E.; Clowes A.W. // Yao Z.; Ruzzo W.L. // Berceli S. // Clowes A.W. // Jeanette J.P. Department of Bioengineering, University of Washington, Seattle, WA, United States // Department of Surgery, University of Washington, Seattle, WA, United States // Department of Pathology, University of Washington, Seattle, WA, United States // Department of Computer Science and Engineering, University of Washington, Seattle, WA, United States // Department of Surgery, University of Florida, Gainesville, FL, United States // Department of Surgery, University of Washington, 1959 NE Pacific St., Seattle, WA 98195-6410, United States // Affiliation unspecified.
CORRESP. AUTHOR: Clowes A.W.
CORRESP. AUTHOR AFFIL: Department of Surgery, University of Washington, 1959 NE Pacific St., Seattle, WA 98195-6410, United States

Journal of Vascular Surgery (J. Vasc. Surg.) (United States) January 1, 2006, 43/1 (150-158)
CODEN: JVSUE ISSN: 07415214
PUBLISHER ITEM IDENTIFIER: S0741521405012577
DOI: 10.1016/j.jvs.2005.08.008
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 60

Objective: Placement in baboons of a distal femoral arteriovenous fistula increases shear stress through aortoiliac polytetrafluoroethylene (PTFE) grafts and induces regression of a preformed neointima. Atrophy of the neointima might be controlled by shear stress-induced genes, including the bone morphogenetic proteins (BMPs). We have investigated the expression and function of BMPs 2, 4, and 5 in the graft neointima and in cultured baboon smooth muscle cells (SMCs). Methods: Baboons received bilateral aortoiliac PTFE grafts and 8 weeks later, a unilateral femoral arteriovenous fistula. Results: Quantitative polymerase chain reaction showed that high shear stress increased BMP2, 4, and 5 messenger RNA (mRNA) in graft intima between 1 and 7 days, while %%%noggin%%% (a BMP inhibitor) mRNA was

decreased. BMP4 most potently (60% inhibition) inhibited platelet-derived growth factor-stimulated SMC proliferation compared with BMP2 and BMP5 (31% and 26%, respectively). BMP4 also increased SMC death by 190% +/- 10%. %%%noggin%%% reversed the antiproliferative and proapoptotic effects of BMP4. Finally, Western blotting confirmed BMP4 protein upregulation by high shear stress at 4 days. BMP4 expression demonstrated by in situ hybridization was confined to endothelial cells. Conclusions: Increased BMPs (particularly BMP4) coupled with decreased %%%noggin%%% may promote high shear stress-mediated graft neointimal atrophy by inhibiting SMC proliferation and increasing SMC death. Clinical Relevance: Pharmacologic therapy to prevent luminal stenosis or restenosis after vascular reconstruction is directed at inhibiting intimal hyperplasia and smooth muscle cell growth. An alternative approach might be to induce intimal atrophy after luminal narrowing has developed. This approach would be particularly useful for treating stenosis in %%%tented%%% vessels or synthetic bypass grafts because intimal hyperplasia is the only mechanism for luminal narrowing. Furthermore, it would permit the physician to treat the population of patients (about 30%) who actually develop a problem with stenosis or restenosis. We have previously provided proof of principle that an established neointima can be induced to atrophy in baboon polytetrafluoroethylene grafts, but not in normal artery, by simply switching from normal to high blood flow and shear stress. In this study, we provide evidence that members of the bone morphogenetic protein family may play a role in this neointimal atrophy. Copyright (c) 2006 by The Society for Vascular Surgery.

2/7/8 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0080929743 EMBASE No: 2005574758
Palliative treatment of oesophageal cancer with dysphagia: More favourable outcome from single-dose internal brachytherapy than from the placement of a self-expanding %%%stent%%%; a multicentre randomised study
Palliatieve behandeling voor slokdarmkanker met passageklachten: Gunstiger uitkomsten van eenmalige inwendige brachytherapie %%%dan%%% van plaatsing van een zelfexpanderende %%%stent%%%; multicentrisch, gerandomiseerd onderzoek
Homs M.Y.V.; Kuipers E.J.; Siersema P.D. // Steyerberg E.W. // Eijkenboom W.M.H. // Tilanus H.W. // Stalpers L.J.A. // Bartelsman J.F.W.M. // Van Lanschot J.J.B. // Wijnderman H.K. // Mulder C.J.J. // Reinders J.G. // Boot H. // Aleman B.M.P.
Afd. Maag-, Darm- en Leverziekten, Erasmus MC, Locatie Dijkzigt, Postbus 2040, 3000 CA Rotterdam, Netherlands // Afd. Klinische Besliskunde, Erasmus MC, Locatie Dijkzigt, Postbus 2040, 3000 CA Rotterdam, Netherlands // Afd. Radiotherapie, Erasmus MC, Locatie Dijkzigt, Postbus 2040, 3000 CA Rotterdam, Netherlands // Afd. Heelkunde, Erasmus MC, Locatie Dijkzigt, Postbus 2040, 3000 CA Rotterdam, Netherlands // Afd. Radiotherapie, Academisch Medisch Centrum, Universiteit van Amsterdam, Amsterdam, Netherlands // Afd. Maag-, Darm- en Leverziekten, Academisch Medisch Centrum, Universiteit van Amsterdam, Amsterdam, Netherlands // Afd. Heelkunde, Academisch Medisch Centrum, Universiteit van Amsterdam, Amsterdam, Netherlands // Universitair Medisch Centrum Utrecht, Afd. Radiotherapie, Utrecht, Netherlands // Ziekenhuis Rijnstate, Afd. Maag-, Darm- en Leverziekten, Arnhem, Netherlands // Arnhems Radiotherapeutisch Instituut, Arnhem, Netherlands // Afd. Maag-, Darm- en Leverziekten, Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, Netherlands // Afd. Radiotherapie, Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, Netherlands
AUTHOR EMAIL: p.siersema@erasmusmc.nl
CORRESP. AUTHOR: Siersema P.D.
CORRESP. AUTHOR AFFIL. Afd. Maag-, Darm- en Leverziekten, Erasmus MC, Locatie Dijkzigt, Postbus 2040, 3000 CA Rotterdam, Netherlands
CORRESP. AUTHOR EMAIL: p.siersema@erasmusmc.nl

Nederlands Tijdschrift voor Geneeskunde (Ned. Tijdschr. Geneeskd.) (Netherlands) December 10, 2005, 149/50 (2800-2806)
CODEN: NETJA ISSN: 00282162
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: Dutch SUMMARY LANGUAGE: English; Dutch
NUMBER OF REFERENCES: 37

Objective. To compare the results of single-dose internal irradiation (brachytherapy) and self-expanding metal %%%stent%%% placement in the palliation of oesophageal obstruction due to cancer of the oesophagus. Design. Randomised trial. Method. In the period from December 1999-Juny 2002, 209 patients with dysphagia due to inoperable carcinoma of the oesophagus were randomised to placement of an Ultraflex %%%stent%%% (n = 108) or single-dose (12 Gy) brachytherapy (n = 101). Primary outcome was relief of dysphagia; secondary outcomes were complications, persistent or recurrent dysphagia, health-related quality of life, and costs. Patients were followed up by monthly home visits from a specialised nurse. Results. Dysphagia improved more rapidly after %%%stent%%% placement than after brachytherapy, but long-term relief of dysphagia was better after brachytherapy. %%%Stent%%% placement resulted in more complications than did brachytherapy (36/108 (33%) versus 21/101 (21%); p = 0.02), due mainly to an increased incidence of late haemorrhage in the %%%stent%%% group (14 versus 5, p = 0.05). The groups did not differ with regard to the incidence of persistent or recurrent dysphagia or median survival (p > 0.20). In the long term, quality-of-life scores were higher in the brachytherapy group. Total medical costs were also similar for both treatments: (euro) 8,215 for %%%stent%%% placement and (euro) 8,135 for brachytherapy. Conclusion. Brachytherapy provided better long-term relief of dysphagia than did %%%stent%%% placement and also produced fewer complications. Brachytherapy is therefore recommended as the preferred treatment for the palliation of dysphagia due to oesophageal cancer.

2/7/9 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0077219632 EMBASE No: 1998129678
Sealing oesophagobronchial fistulae: Better results with selfexpanding %%%stents%%% than with plastic endoprostheses
Afsluiting van oesofagobronchiale fistels: Betere resultaten met zelfexpanderende %%%stents%%% %%%dan%%% met plastic endoprothesen
Kooijman W.; Taal B.G.; Boot H.
Nederlands Kanker Instituut, Antoni van Leeuwenhoek Ziekenhuis, Afd. Gastro-enterologie Mediche O., Plesmanlaan 121, 1066 CX Amsterdam, Netherlands
CORRESP. AUTHOR: Taal B.G.
CORRESP. AUTHOR AFFIL. Nederlands Kanker Instituut, Antoni van Leeuwenhoek Ziekenhuis, Afd. Gastro-enterol. en Med. Oncol., Plesmanlaan 121, 1066 CX Amsterdam, Netherlands

Nederlands Tijdschrift voor Geneeskunde (Ned. Tijdschr. Geneeskd.) (Netherlands) April 11, 1998, 142/15 (845-850)
CODEN: NETJA ISSN: 00282162
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: Dutch SUMMARY LANGUAGE: English; Dutch
NUMBER OF REFERENCES: 21
Objective. To compare the results of plastic endoprostheses and of selfexpanding %%%stents%%% in patients with an oesophagobronchial fistula. Design. Retrospective, descriptive. Setting. Nederlands Kanker Instituut/Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, the Netherlands. Method. Forty-two patients with an oesophagobronchial fistula caused by a malignant turnout in the oesophagus, lungs or mediastinum were fitted with an endoprosthesis during the period 1 January 1991-31 August 1995. Use was made initially of a plastic endoprosthesis with a special tulip funnel (n = 24), later of a coated selfexpanding %%%stent%%% (n = 18). In seven patients, the fistula had been the first manifestation of the tumor. in 35, a recurrence after earlier treatment was involved. The initial characteristics (sex, age, diagnosis, earlier therapy, signs and symptoms) were the same in both groups. Results. Dilatation immediately before insertion of a plastic endoprosthesis was necessary in 23 patients (96%); such dilatation was necessary in four of the patients (22%) fitted with a selfexpanding %%%stent%%%. Complete sealing of the fistula was achieved in 19 (79%) and 15 (83%) patients, respectively. Reoperations were necessary in eight (33%) and three (17%) patients. Early major complications occurred

in four (17%) and two (11%) patients. Conclusion. The selfexpanding %%%stent%%% was faster and earlier to insert than a plastic endoprosthesis, and effective in sealing an oesophagobronchial fistula.

0000638844 (THIS IS THE FULLTEXT)
Medical findings published by Vanderbilt University, U.S. Science Letter, September 25, 2007, p.4770

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 1970

TEXT: 7 SEP 25 - (& NewsRx.net) -- Medical findings published by Vanderbilt University, U.S. This trend article about Vanderbilt University, U.S., is an immediate alert from NewsRx to identify developing directions of research (see also). Study 1: A new study, "Inhibition of epidermal growth factor receptor signaling elevates 15-hydroxyprostaglandin dehydrogenase in non-small-cell lung cancer," is now available. "Evidence indicates that the induction of cyclooxygenase-2 (COX-2) and high prostaglandin E2 (PGE2) levels contribute to the pathogenesis of non-small-cell lung cancer (NSCLC). In addition to overproduction by COX-2, PGE2 concentrations also depend upon the levels of the PGE2 catabolic enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH)," scientists in the United States report. "We find a dramatic down-regulation of PGDH protein in NSCLC cell lines and in resected human tumors when compared with matched normal lung. Affymetrix array analysis of 10 normal lung tissue samples and 49 resected lung tumors revealed a much lower expression of PGDH transcripts in all NSCLC histologic groups. In addition, treatment with the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) erlotinib increased the expression of 15-PGDH in a subset of NSCLC cell lines. This effect may be due in part to an inhibition of the extracellular signal-regulated kinase (ERK) pathway as treatment with mitogen-activated protein kinase kinase (MEK) inhibitor U0126 mimics the erlotinib results. We show by quantitative reverse transcription-PCR that the transcript levels of ZEB1 and Slug transcriptional repressors are dramatically reduced in a responsive cell line upon EGFR and MEK/ERK inhibition. In addition, the Slug protein, but not ZEB1, binds to the PGDH promoter and represses transcription. As these repressors function by recruiting histone deacetylases to promoters, it is likely that PGDH is repressed by an epigenetic mechanism involving histone deacetylation, resulting in increased PGE2 activity in tumors," wrote L. Yang and colleagues, Vanderbilt University, Department of Medicine. The researchers concluded: "This effect is reversible in a subset of NSCLC upon treatment with an EGFR TKI." Yang and colleagues published their study in

Cancer Research (Inhibition of epidermal growth factor receptor signaling elevates 15-hydroxyprostaglandin dehydrogenase in non-small-cell lung cancer. Cancer Research , 2007;67(12):5587-93). For additional information, contact L. Yang, Vanderbilt University School of Medicine, Dept. of Medicine, Nashville, Tennessee 37232 USA. Study 2: Results from the largest study of men with prostate cancer treated with high-dose, intensity modulated radiation therapy (IMRT) show that the majority of patients remain alive with no evidence of disease after an average follow-up period of eight years. The 561 prostate cancer patients treated with IMRT at Memorial Sloan-Kettering Cancer Center were classified into prognostic risk groups. After an average of eight years, 89% of the men in the favorable risk group were disease-free and none of the men in any group developed secondary cancers as a result of the radiation therapy. This report, published in a recent issue of The Journal of Urology , is the first description of long-term outcomes for prostate cancer patients using IMRT. "Our results suggest that IMRT should be the treatment of choice for delivering high-dose, external beam radiotherapy for patients with localized prostate cancer," said Dr. Michael J. Zelefsky, Chief of the Brachytherapy Service at Memorial Sloan-Kettering. "We were able to show long-term safety and long-term efficacy in a very diverse group of prostate cancer patients that we followed - many for as long as ten years. Despite the fact that some patients had an aggressive form of their disease with high Gleason scores and PSA (prostate specific antigen) levels, the overwhelming majority of patients had good tumor control with neither recurrence of their original cancer nor development of second cancers. which one might have expected from the high doses of radiation," he added. Pre-treatment diagnostic evaluations were performed for all of the patients to better define their clinically localized prostate cancer. They were classified into prognostic risk groups as defined by the National Comprehensive Cancer Network guidelines (http://www.nccn.org). These are based on clinical characteristics including age, T stage, Gleason score, PSA level, and pre-treatment with neoadjuvant androgen deprivation. Between April 1996 and January 2000, 561 patients with a median age of 68 (ranging from 46 to 86 years old) were treated with IMRT, an improved form of three-dimensional conformal radiation therapy (3D-CRT), also used in radiotherapy. IMRT uses enhanced planning treatment software that more precisely targets the prostate, allowing the beam of radiation to deliver a high dose (81 Gy) to the tumor target while sparing the adjacent bladder and rectum from exposure to the higher amounts of radiation. Study 3: Vanderbilt University Medical Center has become the first hospital in the region to offer a novel approach to cardiac surgery that includes an immediate post-operative check. Called the Hybrid OR/Cath Lab, the state-of-the-art operating suite houses all the equipment and monitoring devices necessary to perform open-heart surgeries, like coronary bypass, as well as percutaneous coronary interventions and procedures, including angioplasty and %%%stenting%%%. A major advantage will be the ability to perform an angiogram at the end of routine cardiac surgical cases to make sure grafts are in place and blood is flowing properly. Traditionally, a "before picture" was obtained prior to surgery, but an X-ray study after procedures are completed was not the standard of care. John Byrne, MD, likens the Hybrid OR to the change seen in the auto industry after the introduction of safety features like seatbelts and airbags. "We wear our seat belts every day and have air bags. How often does an air bag deploy? Maybe once or twice in your life. I for one am glad it's there when and if it does deploy. The Hybrid OR/CathLab will catch the rare but very important technical error (if it arises). Just like seat belts and air bags save your life in a car accident." Byrne, The William S. Stoney Jr. Professor of Cardiac Surgery and Chair of the Department, said most people had no idea that X-rays of cardiac surgical procedures were not performed post-surgery. He refers to the new operating environment as "sighted" cardiac surgery. "In virtually every reconstructive procedure in medicine and surgery, the medical team takes a "before" and "after" picture," said Byrne. "When we put in a central line, nasogastric tube, a chest tube or an endotracheal tube, when your knee or hip is operated on, when you have gall bladder surgery, you get a before and after picture. When you have your heart valve operated on you have a before and after picture (intraoperative echocardiography). "But for coronary artery surgery there is no "after" picture," he said. "Placing the left internal mammary artery to the left anterior descending coronary artery is perhaps the most important reconstructive procedure any human will ever have in their entire life, yet we don't image the quality of the result. We don't measure it. We've never measured it. This has all changed at Vanderbilt." Although Vanderbilt is one of six centers nationally exploring this idea, it is believed to be the first to put the concept to use. On April 4, the first patient to undergo the newest technology was Robert Metry, a 66-year-old health care attorney from Franklin. Metry was not hesitant to become a pioneer. His triple bypass surgery was done in the new operating suite. "The first thing that interested me was the pure science of having the image done in real time," he said. "They knew that everything was OK when they closed me up. I was also excited that I was getting the A-team." Metry, who has a family history of heart disease, was pleased with the entire experience. "If anyone asked me about the Hybrid OR, I would tell them to do it. You'd want to know as much as possible about the outcome. The doctors can use these outcomes as benchmarks. Measuring outcomes is so important. This is the new direction of medicine." And what has been the delay in introducing this medical breakthrough? Byrne points to the geography of the operating room suites and the cath labs. In most hospitals these facilities are located in separate areas. At Vanderbilt, the OR suites are on the third floor, while the cath labs are on the first floor. Orchestrating the transport of patients requiring both open-heart surgery and interventional procedures is

cumbersome and often inefficient, with lag times of up to seven hours. And the need for an X-ray of the procedure would also require transporting patients from the third to the first floor. Finally, if any surgical intervention is needed after an X-ray is obtained, the patient would be transported back to the OR. Previously at Vanderbilt and still done elsewhere, physicians use what is labeled soft measurements to check a patient's recovery status. These tools include flow probes, EKGs, Echos and ultrasounds which all help determine blood flow. They are not effective when looking at the anatomy of the heart, which is vital when checking for successful grafting and other cardiac procedures, Byrne said. Another familiar scenario before the Hybrid OR - patients with aortic stenosis or a blockage of the aortic valve with blockage in the right coronary artery; they could have the right coronary artery %%%stented%%% in the cath lab and then be transported to the OR for a minimally invasive valve surgery. It required procedures in two separate locations or at two separate times - both of which require patients to leave and re-enter sterile fields. The Hybrid OR allows them both to be done at the same time, boosting patient safety. Now that Vanderbilt has opened the Hybrid OR suites, a "one-stop shop" as Byrne refers to it, will create a new model for treating patients. "The key barrier-to-entry into this new realm has not been equipment or the space. The real barrier-to-entry is collaboration and teamwork between cardiology and cardiac surgery; not just among physicians but also among the OR team and the cath lab team. %%%Dan%%% Brinkman, RN, director of the cath lab, has been instrumental in building the team." At Vanderbilt the teams have been combined to provide a new standard of care, Byrne said. Hybrid procedures will become more common as medical centers begin to see an increase in more complex heart disease patients. The need to image results to measure outcomes will become necessary in order to be more efficient, effective and safe. "I know this is right," Byrne said. "I would want it for me or a family member. When you know it's right for the patients, you never lose. This will offer patients, families and referring physicians not only image-guided surgery, but also the ability to provide minimally invasive cardiac surgery combined with percutaneous coronary interventions." David Zhao, MD, assistant professor of Medicine and director of the cardiac catheterization lab and interventional cardiology, agrees. "First and foremost it provides better care for the patient," he said. "They receive the best of both worlds through the collaboration of interventional cardiology and cardiac surgery." "The mammary artery has a lot of branches and is the only revascularization conduit that prolongs life," Zhao said. "In time, that graft would have become occluded and it would not have been discovered for several months or even years if it was not for the Hybrid OR. By doing the post-bypass angiography, you are 100% sure the patient has perfect grafts." This article was prepared by Science Letter editors from staff and other reports. Copyright 2007, Science Letter via & NewsRx.net.

2/7/11 (Item 2 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports
(c) 2008 NewsRx. All rts. reserv.

0000601221 (THIS IS THE FULLTEXT)
New findings from Vanderbilt University, U.S., detailed
Biotech Business Week. August 20, 2007, p.2827

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 1882

TEXT: New findings from Vanderbilt University, U.S., detailed. This trend article about Vanderbilt University, U.S., is an immediate alert from NewsRx to identify developing directions of research. Study 1: Scientists discuss in "The sedation of critically ill adults: Part 1: Assessment. The first in a two-part series focuses on assessing sedated patients in the ICU" new findings in delirium. According to a study from the United States, "The prevention or treatment of pain, anxiety, and delirium in the ICU is an important goal. But achieving a balance between sedation and analgesia, especially in critically ill patients on mechanical ventilation, can be challenging." "Both under-and oversedation carry serious risks. In 2002 the Society of Critical Care Medicine, along with the American Society of Health-System Pharmacists, updated recommendations in its clinical practice guidelines for the sustained use of sedatives and analgesics in adults. This two-part series examines those recommendations that relate to sedation assessment and management, as well as the current literature. This month Part 1 also reviews pertinent recommendations concerning pain and delirium and discusses tools for assessing pain, delirium, and sedation. In August Part 2 will explore pharmacologic and nonpharmacologic management of anxiety and agitation in critically ill patients. The prevention or treatment of pain, anxiety, and delirium in the ICU is an important goal. But achieving a balance between sedation and analgesia, especially in critically ill patients on mechanical ventilation, can be challenging. Both under-and oversedation carry serious risks. In 2002 the Society of Critical Care Medicine, along with the American Society of Health-System Pharmacists, updated recommendations in its clinical practice guidelines for the sustained use of sedatives and analgesics in adults. This two-part series examines those recommendations that relate to sedation assessment and management, as well as the current literature. This month Part 1 also reviews pertinent recommendations concerning pain and delirium and discusses tools for assessing pain, delirium, and sedation," wrote B.T. Pun and colleagues, Vanderbilt University. The researchers concluded: "In August Part 2 will explore pharmacologic and nonpharmacologic management of anxiety and agitation in critically ill patients." Pun and colleagues published their study in American Journal of Nursing (The sedation of critically ill adults: Part 1: Assessment. The first in a two-part series focuses on assessing sedated patients in the ICU.

American Journal of Nursing , 2007;107(7):40-8; quiz 49). For more information, contact B.T. Pun, Vanderbilt University Medical Center, Nashville, TN USA.. Study 2: Vanderbilt University Medical Center has become the first hospital in the region to offer a novel approach to cardiac surgery that includes an immediate post-operative check. Called the Hybrid OR/Cath Lab, the state-of-the-art operating suite houses all the equipment and monitoring devices necessary to perform open-heart surgeries, like coronary bypass, as well as percutaneous coronary interventions and procedures, including angioplasty and %%%stenting%%%. A major advantage will be the ability to perform an angiogram at the end of routine cardiac surgical cases to make sure grafts are in place and blood is flowing properly. Traditionally, a "before picture" was obtained prior to surgery, but an X-ray study after procedures are completed was not the standard of care. John Byrne, MD, likens the Hybrid OR to the change seen in the auto industry after the introduction of safety features like seatbelts and airbags. "We wear our seat belts every day and have air bags. How often does an air bag deploy? Maybe once or twice in your life. I for one am glad it's there when and if it does deploy. The Hybrid OR/CathLab will catch the rare but very important technical error (if it arises). Just like seat belts and air bags save your life in a car accident." Byrne, The William S. Stoney Jr. Professor of Cardiac Surgery and Chair of the Department, said most people had no idea that X-rays of cardiac surgical procedures were not performed post-surgery. He refers to the new operating environment as "sighted" cardiac surgery. "In virtually every reconstructive procedure in medicine and surgery, the medical team takes a "before" and "after" picture," said Byrne. "When we put in a central line, nasogastric tube, a chest tube or an endotracheal tube, when your knee or hip is operated on, when you have gall bladder surgery, you get a before and after picture. When you have your heart valve operated on you have a before and after picture (intraoperative echocardiography). "But for coronary artery surgery there is no "after" picture," he said. "Placing the left internal mammary artery to the left anterior descending coronary artery is perhaps the most important reconstructive procedure any human will ever have in their entire life, yet we don't image the quality of the result. We don't measure it. We've never measured it. This has all changed at Vanderbilt." Although Vanderbilt is one of six centers nationally exploring this idea, it is believed to be the first to put the concept to use. On April 4, the first patient to undergo the newest technology was Robert Metry, a 66-year-old health care attorney from Franklin. Metry was not hesitant to become a pioneer. His triple bypass surgery was done in the new operating suite. "The first thing that interested me was the pure science of having the image done in real time," he said. "They knew that everything was OK when they closed me up. I was also excited that I was getting the A-team."

Metry, who has a family history of heart disease, was pleased with the entire experience. "If anyone asked me about the Hybrid OR, I would tell them to do it. You'd want to know as much as possible about the outcome. The doctors can use these outcomes as benchmarks. Measuring outcomes is so important. This is the new direction of medicine." And what has been the delay in introducing this medical breakthrough? Byrne points to the geography of the operating room suites and the cath labs. In most hospitals these facilities are located in separate areas. At Vanderbilt, the OR suites are on the third floor, while the cath labs are on the first floor. Orchestrating the transport of patients requiring both open-heart surgery and interventional procedures is cumbersome and often inefficient, with lag times of up to seven hours. And the need for an X-ray of the procedure would also require transporting patients from the third to the first floor. Finally, if any surgical intervention is needed after an X-ray is obtained, the patient would be transported back to the OR. Previously at Vanderbilt and still done elsewhere, physicians use what is labeled soft measurements to check a patient's recovery status. These tools include flow probes, EKGs, Echos and ultrasounds which all help determine blood flow. They are not effective when looking at the anatomy of the heart, which is vital when checking for successful grafting and other cardiac procedures, Byrne said. Another familiar scenario before the Hybrid OR - patients with aortic stenosis or a blockage of the aortic valve with blockage in the right coronary artery; they could have the right coronary artery %%%stented%%% in the cath lab and then be transported to the OR for a minimally invasive valve surgery. It required procedures in two separate locations or at two separate times - both of which require patients to leave and re-enter sterile fields. The Hybrid OR allows them both to be done at the same time, boosting patient safety. Now that Vanderbilt has opened the Hybrid OR suites, a "one-stop shop" as Byrne refers to it, will create a new model for treating patients. "The key barrier-to-entry into this new realm has not been equipment or the space. The real barrier-to-entry is collaboration and teamwork between cardiology and cardiac surgery; not just among physicians but also among the OR team and the cath lab team. %%%Dan%%% Brinkman, RN, director of the cath lab, has been instrumental in building the team." At Vanderbilt the teams have been combined to provide a new standard of care, Byrne said. Hybrid procedures will become more common as medical centers begin to see an increase in more complex heart disease patients. The need to image results to measure outcomes will become necessary in order to be more efficient, effective and safe. "I know this is right," Byrne said. "I would want it for me or a family member. When you know it's right for the patients, you never lose. This will offer patients, families and referring physicians not only image-guided surgery, but also the ability to provide minimally invasive cardiac surgery combined with percutaneous coronary interventions." David Ziaso, MD, assistant professor of Medicine and director of the cardiac catheterization lab and interventional cardiology, agrees. "First and foremost it provides better care for the patient," he said. "They receive the best of both worlds through the collaboration of interventional cardiology and cardiac surgery." Study 3: Carcinogens induce genome-wide loss of heterozygosity in normal stem cells without persistent chromosomal instability. According to a study from the United States, "Widespread losses of heterozygosity (LOH) in human cancer have been thought to result from chromosomal instability caused by mutations affecting DNA repair/genome maintenance. However, the origin of LOH in most tumors is unknown." "The present study examined the ability of carcinogenic agents to induce LOH at 53 sites throughout the genome of normal diploid mouse ES cells. Brief exposures to nontoxic levels of methylnitrosourea, diepoxybutane, mitomycin C, hydroxyurea, doxorubicin, and UV light stimulated LOH at all loci at frequencies ranging from 1-8x10 -3 per cell (10-123 times higher than in untreated cells). "This greatly exceeds the frequencies at which these agents have been reported to induce point mutations and is comparable to the rates of LOH observed in ES cells lacking the gene responsible for Bloom syndrome, an inherited DNA repair defect that results in greatly increased risk of cancer," investigators wrote. "These results suggest that LOH contributes significantly to the carcinogenicity of a variety of mutagens and raises the possibility that genome-wide LOH observed in some human cancers may reflect prior exposure to genotoxic agents rather than a state of chromosomal instability during the carcinogenic process." S.L. Donahue and colleagues at Vanderbilt University in Nashville said. Donahue concluded, "Finally, as a practical matter, chemically induced LOH is expected to enhance the recovery of homozygous recessive mutants from phenotype-based genetic screens in mammalian cells." Donahue and colleagues published their study in Proceedings of the National Academy of Sciences of the United States of America (Carcinogens induce genome-wide loss of heterozygosity in normal stem cells without persistent chromosomal instability. Proc Natl Acad Sci USA, 2006;103(31):11642-11646). For more information, contact H.E. Ruley, Vanderbilt University, School Medical, Medical Center N, Dept. of Microbiology & Immunology, Room AA4210, 1161 21st Avenue S. Nashville, TN 37232, USA. Keywords: Nashville, Tennessee, United States, Carcinogenesis. Genome Stability, Mutagens, Loss of Heterozygosity, Stem Cells. This article was prepared by Biotech Business Week editors from staff and other reports. Copyright 2007, Biotech Business Week via NewsRx.com & NewsRx.net. (c)Copyright 2007, Pharma Business Week via NewsRx.com & NewsRx.net

0000554728 (THIS IS THE FULLTEXT)
Vanderbilt University, U.S., researchers publish latest findings
Life Science Weekly, June 26, 2007, p.4771

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 1826

TEXT: Vanderbilt University, U.S., researchers publish latest findings. This trend article about Vanderbilt University, U.S., is an immediate alert from NewsRx to identify developing directions of research. Study 1: A report, "Yin Yang 1 enhances cyclooxygenase-2 gene expression in macrophages," is newly published data in American Journal of Physiology - Lung Cellular and Molecular Physiology . According to a study from the United States, "Expression of cyclooxygenase-2 (COX-2) is associated with the pathogenesis of inflammation and various cancers, including lung cancer. Yin Yang 1 (YY1) is a zinc-finger transcription factor that interacts with histone acetyltransferases and deacetylases for its transcriptional activity and also is involved in inflammation and tumorigenesis." "We investigated whether YY1 regulates COX-2 expression. We located a possible YY1 binding site proximal to the transcription initiation site of the COX-2 promoter. Electrophoretic mobility shift assays show that YY1 bound to the putative YY1 site in vitro. To show biological relevance, we performed chromatin immunoprecipitation assays showing that lipopolysaccharide (LPS) treatment induced YY1 binding to the cognate site in the endogenous COX-2 promoter. Overexpression of YY1 in macrophages treated with either LPS or live

Pseudomonas aeruginosa increased COX-2 transcriptional activity. Furthermore, YY1 enhanced COX-2 protein expression and prostaglandin D(2) production elicited by LPS treatment. Mechanistically, we observed that LPS treatment resulted in disruption of an interaction between YY1 and p300, a histone acetyltransferase, but did not affect the interaction between YY1 and histone deacetylase 1/2," wrote M. Joo and colleagues, Vanderbilt University. The researchers concluded: "These data suggest that in response to LPS, YY1 dissociates from p300 and binds to the COX-2 promoter, contributing to COX-2 expression in an inflammatory milieu." Joo and colleagues published the results of their research in American Journal of Physiology - Lung Cellular and Molecular Physiology (Yin Yang 1 enhances cyclooxygenase-2 gene expression in macrophages. American Journal of Physiology - Lung Cellular and Molecular Physiology , 2007;292(5):L1219-26). For additional information, contact M. Joo, Division of Allergy, Dept. of Medicine, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-2650 USA. Study 2: Vanderbilt University Medical Center has become the first hospital in the region to offer a novel approach to cardiac surgery that includes an immediate post-operative check. Called the Hybrid OR/Cath Lab, the state-of-the-art operating suite houses all the equipment and monitoring devices necessary to perform open-heart surgeries, like coronary bypass, as well as percutaneous coronary interventions and procedures, including angioplasty and %%%stenting%%%. A major advantage will be the

ability to perform an angiogram at the end of routine cardiac surgical cases to make sure grafts are in place and blood is flowing properly. Traditionally, a "before picture" was obtained prior to surgery, but an X-ray study after procedures are completed was not the standard of care. John Byrne, MD, likens the Hybrid OR to the change seen in the auto industry after the introduction of safety features like seatbelts and airbags. "We wear our seat belts every day and have air bags. How often does an air bag deploy? Maybe once or twice in your life. I for one am glad it's there when and if it does deploy. The Hybrid OR/CathLab will catch the rare but very important technical error (if it arises). Just like seat belts and air bags save your life in a car accident," Byrne, The William S. Stoney Jr. Professor of Cardiac Surgery and Chair of the Department, said most people had no idea that X-rays of cardiac surgical procedures were not performed post-surgery. He refers to the new operating environment as "sighted" cardiac surgery. "In virtually every reconstructive procedure in medicine and surgery, the medical team takes a "before" and "after" picture," said Byrne. "When we put in a central line, nasogastric tube, a chest tube or an endotracheal tube, when your knee or hip is operated on, when you have gall bladder surgery, you get a before and after picture. When you have your heart valve operated on you have a before and after picture (intraoperative echocardiography). "But for coronary artery surgery there is no "after" picture," he said. "Placing the left internal mammary artery to the left anterior descending coronary artery is perhaps the most important reconstructive procedure any human will ever have in their entire life, yet we don't image the quality of the result. We don't measure it. We've never measured it. This has all changed at Vanderbilt." Although Vanderbilt is one of six centers nationally exploring this idea, it is believed to be the first to put the concept to use. On April 4, the first patient to undergo the newest technology was Robert Metry, a 66-year-old health care attorney from Franklin. Metry was not hesitant to become a pioneer. His triple bypass surgery was done in the new operating suite. "The first thing that interested me was the pure science of having the image done in real time," he said. "They knew that everything was OK when they closed me up. I was also excited that I was getting the A-team." Metry, who has a family history of heart disease, was pleased with the entire experience. "If anyone asked me about the Hybrid OR, I would tell them to do it. You'd want to know as much as possible about the outcome. The doctors can use these outcomes as benchmarks. Measuring outcomes is so important. This is the new direction of medicine." And what has been the delay in introducing this medical breakthrough? Byrne points to the geography of the operating room suites and the cath labs. In most hospitals these facilities are located in separate areas. At Vanderbilt, the OR suites are on the third floor, while the cath labs are on the first floor. Orchestrating the transport of patients requiring both open-heart surgery and interventional procedures is cumbersome and often inefficient, with lag times of up to seven hours. And the need for an X-ray of the procedure would also require transporting patients from the third to the first floor. Finally, if any surgical intervention is needed after an X-ray is obtained, the patient would be transported back to the OR. Previously at Vanderbilt and still done elsewhere, physicians use what is labeled soft measurements to check a patient's recovery status. These tools include flow probes, EKGs, Echos and ultrasounds which all help determine blood flow. They are not effective when looking at the anatomy of the heart, which is vital when checking for successful grafting and other cardiac procedures, Byrne said. Another familiar scenario before the Hybrid OR - patients with aortic stenosis or a blockage of the aortic valve with blockage in the right coronary artery, they could have the right coronary artery %%%stented%%% in the cath lab and then be transported to the OR for a minimally invasive valve surgery. It required procedures in two separate locations or at two separate times - both of which require patients to leave and re-enter sterile fields. The Hybrid OR allows them both to be done at the same time, boosting patient safety. Now that Vanderbilt has opened the Hybrid OR suites, a "one-stop shop" as Byrne refers to it, will create a new model for treating patients. "The key barrier-to-entry into this new realm has not been equipment or the space. The real barrier-to-entry is collaboration and teamwork between cardiology and cardiac surgery; not just among physicians but also among the OR team and the cath lab team. %%%Dan%%% Brinkman, RN, director of the cath lab, has been instrumental in building the team." At Vanderbilt the teams have been combined to provide a new standard of care, Byrne said. Hybrid procedures will become more common as medical centers begin to see an increase in more complex heart disease patients. The need to image results to measure outcomes will become necessary in order to be more efficient, effective and safe. "I know this is right," Byrne said. "I would want it for me or a family member. When you know it's right for the patients, you never lose. This will offer patients, families and referring physicians not only image-guided surgery, but also the ability to provide minimally invasive cardiac surgery combined with percutaneous coronary interventions." David Zhao, MD, assistant professor of Medicine and director of the cardiac catheterization lab and interventional cardiology, agrees: "First and foremost it provides better care for the patient," he said. "They receive the best of both worlds through the collaboration of interventional cardiology and cardiac surgery." Study 3: Carcinogens induce genome-wide loss of heterozygosity in normal stem cells without persistent chromosomal instability. According to a study from the United States, "Widespread losses of heterozygosity (LOH) in human cancer have been thought to result from chromosomal instability caused by mutations affecting DNA repair/genome maintenance. However, the origin of LOH in most tumors is unknown." "The present study examined the ability of carcinogenic agents to induce LOH at 53 sites throughout the genome of normal diploid mouse ES cells. Brief exposures to nontoxic levels of methylnitrosourea, diepoxybutane, mitomycin C, hydroxyurea, doxorubicin, and UV light stimulated LOH at all loci at frequencies ranging from 1-8x10 -3 per cell (10-123 times higher than in untreated cells). "This greatly exceeds the frequencies at which these agents have been reported to induce point mutations and is comparable to the rates of LOH observed in ES cells lacking the gene responsible for Bloom syndrome, an inherited DNA repair defect that results in greatly increased risk of cancer," investigators wrote. "These results suggest that LOH contributes significantly to the carcinogenicity of a variety of mutagens and raises the possibility that genome-wide LOH observed in some human cancers may reflect prior exposure to genotoxic agents rather than a state of chromosomal instability during the carcinogenic process," S.L. Donahue and colleagues at Vanderbilt University in Nashville said. Donahue concluded, "Finally, as a practical matter, chemically induced LOH is expected to enhance the recovery of homozygous recessive mutants from phenotype-based genetic screens in mammalian cells." Donahue and colleagues published their study in Proceedings of the National Academy of Sciences of the United States of America (Carcinogens induce genome-wide loss of heterozygosity in normal stem cells without persistent chromosomal instability. Proc Natl Acad Sci USA, 2006;103(31):11642-11646). For more information, contact H.E. Ruley, Vanderbilt University, School Medical, Medical Center N, Dept. of Microbiology & Immunology, Room AA4210, 1161 21st Avenue S, Nashville, TN 37232, USA. Keywords: Nashville, Tennessee, United States, Carcinogenesis, Genome Stability, Mutagens, Loss of Heterozygosity, Stem Cells. This article was prepared by Life Science Weekly editors from staff and other reports. Copyright 2007, Life Science Weekly via NewsRx.com & NewsRx.net. (c)Copyright 2007, Life Science Weekly via NewsRx.com & NewsRx.net

0000544138 (THIS IS THE FULLTEXT)
Researchers from Vanderbilt University, U.S., provide details of new studies and findings
Biotech Business Week, June 11, 2007, p.1208

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 1843

TEXT: Researchers from Vanderbilt University, U.S., provide details of new studies and findings. This trend article about Vanderbilt University, U.S., is an immediate alert from NewsRx to identify developing directions of research. Study 1: Data detailed in "Task switching versus cue switching: using transition cuing to disentangle sequential effects in task-switching performance" have been presented. According to recent research from the United States, "Recent methodological advances have

allowed researchers to address confounds in the measurement of task-switch costs in task-switching performance by dissociating cue switching from task switching. For example, in the transition-cuing procedure, which involves presenting cues for task transitions rather than for tasks, cue transitions (cue switches and cue repetitions) and task transitions (task switches and task repetitions) can be examined in a complete factorial design." "Transition cuing removes the confound between cue transitions and first-order task transitions, but it introduces a confound between cue transitions and longer task sequences. In the present study, transition cuing was studied with two cues per transition (REPEAT and AGAIN for task repetitions; SWITCH and CHANGE for task switches), enabling a partial deconfounding of cue transitions and task sequences. Two experiments revealed robust sequential effects, with higher order task transitions affecting performance when cue transitions were held constant and with cue transitions affecting performance when task sequences were held constant," wrote D.W. Schneider and colleagues, Vanderbilt University, Department of Psychology. The researchers concluded: "Methodological and theoretical implications of these findings for research on task switching are discussed." Schneider and colleagues published their study in the Journal of Experimental Psychology (Task switching versus cue switching: using transition cuing to disentangle sequential effects in task-switching performance. Journal of Experimental Psychology, 2007;33(2):370-8). For additional information, contact D.W. Schneider, Vanderbilt University, Dept. of Psychology, Nashville, TN 37203 USA. Study 2: Vanderbilt University Medical Center has become the first hospital in the region to offer a novel approach to cardiac surgery that includes an immediate post-operative check. Called the Hybrid OR/Cath Lab, the state-of-the-art operating suite houses all the equipment and monitoring devices necessary to perform open-heart surgeries, like coronary bypass, as well as percutaneous coronary interventions and procedures, including angioplasty and %%%stenting%%%. A major advantage will be the ability to perform an angiogram at the end of routine cardiac surgical cases to make sure grafts are in place and blood is flowing properly. Traditionally, a "before picture" was obtained prior to surgery, but an X-ray study after procedures are completed was not the standard of care. John Byrne, MD, likens the Hybrid OR to the change seen in the auto industry after the introduction of safety features like seatbelts and airbags. "We wear our seat belts every day and have air bags. How often does an air bag deploy? Maybe once or twice in your life. I for one am glad it's there when and if it does deploy. The Hybrid OR/CathLab will catch the rare but very important technical error (if it arises). Just like seat belts and air bags save your life in a car accident." Byrne, The William S. Stoney Jr. Professor of Cardiac Surgery and Chair of the Department, said most people had no idea that X-rays of cardiac surgical procedures were not performed post-surgery. He refers to the new operating environment as "sighted" cardiac surgery. "In virtually every reconstructive procedure in medicine and surgery, the medical team takes a "before" and "after" picture," said Byrne. "When we put in a central line, nasogastric tube, a chest tube or an endotracheal tube, when your knee or hip is operated on, when you have gall bladder surgery, you get a before and after picture. When you have your heart valve operated on you have a before and after picture (intraoperative echocardiography). "But for coronary artery surgery there is no "after" picture," he said. "Placing the left internal mammary artery to the left anterior descending coronary artery is perhaps the most important reconstructive procedure any human will ever have in their entire life, yet we don't image the quality of the result. We don't measure it. We've never measured it. This has all changed at Vanderbilt." Although Vanderbilt is one of six centers nationally exploring this idea, it is believed to be the first to put the concept to use. On April 4, the first patient to undergo the newest technology was Robert Metry, a 66-year-old health care attorney from Franklin. Metry was not hesitant to become a pioneer. His triple bypass surgery was done in the new operating suite. "The first thing that interested me was the pure science of having the image done in real time," he said. "They knew that everything was OK when they closed me up. I was also excited that I was getting the A-team." Metry, who has a family history of heart disease, was pleased with the entire experience. "If anyone asked me about the Hybrid OR, I would tell them to do it. You'd want to know as much as possible about the outcome. The doctors can use these outcomes as benchmarks. Measuring outcomes is so important. This is the new direction of medicine." And what has been the delay in introducing this medical breakthrough? Byrne points to the geography of the operating room suites and the cath labs. In most hospitals these facilities are located in separate areas. At Vanderbilt, the OR suites are on the third floor, while the cath labs are on the first floor. Orchestrating the transport of patients requiring both open-heart surgery and interventional procedures is cumbersome and often inefficient, with lag times of up to seven hours. And the need for an X-ray of the procedure would also require transporting patients from the third to the first floor. Finally, if any surgical intervention is needed after an X-ray is obtained, the patient would be transported back to the OR. Previously at Vanderbilt and still done elsewhere, physicians use what is labeled soft measurements to check a patient's recovery status. These tools include flow probes, EKGs, Echos and ultrasounds which all help determine blood flow. They are not effective when looking at the anatomy of the heart, which is vital when checking for successful grafting and other cardiac procedures, Byrne said. Another familiar scenario before the Hybrid OR - patients with aortic stenosis or a blockage of the aortic valve with blockage in the right coronary artery; they could have the right coronary artery %%%tented%%% in the cath lab and then be transported to the OR for a minimally invasive valve surgery. It required procedures in two separate locations or at two separate times - both of which require patients to leave and re-enter sterile fields. The Hybrid OR allows them both to be done at the same time, boosting patient safety. Now that Vanderbilt has opened the Hybrid OR suites, a "one-stop shop" as Byrne refers to it, will create a new model for treating patients. "The key barrier-to-entry into this new realm has not been equipment or the space. The real barrier-to-entry is collaboration and teamwork between cardiology and cardiac surgery; not just among physicians but also among the OR team and the cath lab team. %%%Dan%%% Brinkman, RN, director of the cath lab, has been instrumental in building the team." At Vanderbilt the teams have been combined to provide a new standard of care, Byrne said. Hybrid procedures will become more common as medical centers begin to see an increase in more complex heart disease patients. The need to image results to measure outcomes will become necessary in order to be more efficient, effective and safe. "I know this is right," Byrne said. "I would want it for me or a family member. When you know it's right for the patients, you never lose. This will offer patients, families and referring physicians not only image-guided surgery, but also the ability to provide minimally invasive cardiac surgery combined with percutaneous coronary interventions." David Zhao, MD, assistant professor of Medicine and director of the cardiac catheterization lab and interventional cardiology, agrees. "First and foremost it provides better care for the patient," he said. "They receive the best of both worlds through the collaboration of interventional cardiology and cardiac surgery." Study 3: Recent research from the United States has reported on the characterization of ubiquitin thiolester formation of UBE2Q2 (UBCi), a novel ubiquitin-conjugating enzyme with implantation site-specific expression. "We recently identified a differentially expressed gene in implantation stage rabbit endometrium encoding a new member of the ubiquitin-conjugating enzyme family designated UBE2Q2 (also known as UBCi). Its unusually high molecular mass, novel N-terminus extension, and highly selective pattern of mRNA expression suggest a specific function in implantation. "This study analyzes its relationship to the E2 ubiquitin-conjugating enzyme superfamily, investigates its enzymatic activity, and examines its localization in implantation site endometrium," wrote M.H. Melner and colleagues, Vanderbilt University. "Construction of a dendrogram indicated that UBE2Q2 is homologous to the UBC2 family of enzymes, and isoforms are present in a broad range of species. In vitro enzymatic assays of ubiquitin thiolester formation demonstrated that UBE2Q2 is a functional ubiquitin-conjugating enzyme. "The Km for transfer of ubiquitin thiolester from E1 to UBE2Q2 is 817 nM compared to 100 nM for other E2 paralogs; this suggests that the unique amino terminal domain of UBE2Q2 confers specific functional differences," wrote the researchers. "Affinity-purified antibodies prepared with purified recombinant UBE2Q2 showed that the protein was undetectable by immunoblot analysis in endometrial lysates from estrous and Day 6 3/4 pregnant (blastocyst attachment stage) rabbits but was expressed in both mesometrial and antimesometrial implantation site endometrium of Day 8 pregnant animals. "No expression was detected in adjacent interimplantation sites. Immunohistochemistry demonstrated UBE2Q2 expression exclusively in mesometrial and antimesometrial endometrial luminal epithelial cells of the Day 8 implantation chamber," the scientists observed. "Immunohistochemical

localization of ubiquitin mirrored UBE2Q2 expression, with low-to-undetectable levels in implantation sites of Day 6 3/4 pregnant endometrium but high levels in luminal epithelial cells of Day 8 pregnant endometrium," the authors noted. They concluded, "This implantation site-specific expression of UBE2Q2 in luminal epithelial cells could play major roles in orchestrating differentiation events through the modification of specific protein substrates." Melner and colleagues published their study in

n Biology of Reproduction (Demonstration of ubiquitin thiolester formation of UBE2Q2 (UBCi), a novel ubiquitin-conjugating enzyme with implantation site-specific expression. Biol Reprod, 2006;75(3):395-406). For additional information, contact M.H. Melner, Vanderbilt University, School of Medicine, Department of Obstetrics & Gynecology, Nashville, TN 37232, USA. Keywords: Nashville, Tennessee, United States, Enzymology, Female Reproductive Tract, Gynecology, Implantation, Obstetrics, Pregnancy, Ubiquitin Thiolester, Conjugating Enzymes. This article was prepared by Biotech Business Week editors from staff and other reports. Copyright 2007, Biotech Business Week via NewsRx.com & NewsRx.net.
(c)Copyright 2007, Life Science Weekly via NewsRx.com & NewsRx.net

2/7/14 (Item 5 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports
(c) 2008 NewsRx. All rts. reserv.

0000529297 (THIS IS THE FULLTEXT)
Findings from Vanderbilt University...U.S., research reported
Pharma Business Week, May 21, 2007, p.2561

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 1910

TEXT: Findings from Vanderbilt University, U.S., research reported. This trend article about Vanderbilt University, U.S., is an immediate alert from NewsRx to identify developing directions of research. Study 1: Data detailed in "The histopathology of fatal untreated human respiratory syncytial virus infection" have been presented. "The pathology of respiratory syncytial virus (RSV) infection was evaluated 1 day after an outpatient diagnosis of RSV in a child who died in a motor vehicle accident. We then identified 11 children with bronchiolitis from the Vanderbilt University autopsy log between 1925 and 1959 who met criteria for possible RSV infection in the preantiserum era," scientists writing in the journal Modern Pathology report. "Their tissue was re-embedded and evaluated by routine hematoxylin and eosin and PAS staining and immunostaining with RSV-specific antibodies. Tissue from three cases was immunostain-positive for RSV antigen and was examined in detail. Small bronchiole epithelium was circumferentially infected, but basal cells were spared. Both type 1 and 2 alveolar pneumocytes were also infected. Although, not possible for archival cases, tissue from the index case was evaluated by immunostaining with antibodies to define the cellular components of the inflammatory response. Inflammatory infiltrates were centered on bronchial and pulmonary arterioles and consisted of primarily CD69+ monocytes, CD3+ double-negative T cells, CD8+ T cells, and neutrophils. The neutrophil distribution was predominantly between arterioles and airways, while the mononuclear cell distribution was in both airways and lung parenchyma. Most inflammatory cells were concentrated submucular to the airway, but many cells traversed the smooth muscle into the airway epithelium and lumen. Airway obstruction was a prominent feature in all cases attributed to epithelial and inflammatory cell debris mixed with fibrin, mucus, and edema, and compounded by compression from hyperplastic lymphoid follicles," wrote J.E. Johnson and colleagues, Vanderbilt University, Department of Pathology. The researchers concluded: "These findings inform our understanding of RSV pathogenesis and may facilitate the development of new approaches for prevention and treatment." Johnson and colleagues published their study in

n Modern Pathology (The histopathology of fatal untreated human respiratory syncytial virus infection. Modern Pathology, 2007;20(1):108-19). Additional information can be obtained by contacting J.E. Johnson, Vanderbilt University School of Medicine, Dept. of Pathology, Nashville, TN USA. Study 2: Vanderbilt University Medical Center has become the first hospital in the region to offer a novel approach to cardiac surgery that includes an immediate post-operative check. Called the Hybrid OR/Cath Lab, the state-of-the-art operating suite houses all the equipment and monitoring devices necessary to perform open-heart surgeries, like coronary bypass, as well as percutaneous coronary interventions and procedures, including angioplasty and %%%stenting%%%. A major advantage will be the ability to perform an angiogram at the end of routine cardiac surgical cases to make sure grafts are in place and blood is flowing properly. Traditionally, a "before picture" was obtained prior to surgery, but an X-ray study after procedures are completed was not the standard of care. John Byrne, MD, likens the Hybrid OR to the change seen in the auto industry after the introduction of safety features like seatbelts and airbags. "We wear our seat belts every day and have air bags. How often does an air bag deploy? Maybe once or twice in your life. I for one am glad it's there when and if it does deploy. The Hybrid OR/CathLab will catch the rare but very important technical error (if it arises). Just like seat belts and air bags save your life in a car accident." Byrne, The William S. Stoney Jr. Professor of Cardiac Surgery and Chair of the Department, said most people had no idea that X-rays of cardiac surgical procedures were not performed post-surgery. He refers to the new operating environment as "sighted" cardiac surgery. "In virtually every reconstructive procedure in medicine and surgery, the medical team takes a "before" and "after" picture," said Byrne. "When we put in a central line, nasogastric tube, a chest tube or an endotracheal tube, when your knee or hip is operated on, when you have gall bladder surgery, you get a before and after picture. When you have your heart valve operated on you have a before and after picture (intraoperative echocardiography). "But for coronary artery surgery there is no "after" picture," he said. "Placing the left internal mammary artery to the left anterior descending coronary artery is perhaps the most important reconstructive procedure any human will ever have in their entire life, yet we don't image the quality of the result. We don't measure it. We've never measured it. This has all changed at Vanderbilt." Although Vanderbilt is one of six centers nationally exploring this idea, it is believed to be the first to put the concept to use. On April 4, the first patient to undergo the newest technology was Robert Metry, a 66-year-old health care attorney from Franklin. Metry was not hesitant to become a pioneer. His triple bypass surgery was done in the new operating suite. "The first thing that interested me was the pure science of having the image done in real time," he said. "They knew that everything was OK when they closed me up. I was also excited that I was getting the A-team." Metry, who has a family history of heart disease, was pleased with the entire experience. "If anyone asked me about the Hybrid OR, I would tell them to do it. You'd want to know as much as possible about the outcome. The doctors can use these outcomes as benchmarks. Measuring outcomes is so important. This is the new direction of medicine." And what has been the delay in introducing this medical breakthrough? Byrne points to the geography of the operating room suites and the cath labs. In most hospitals these facilities are located in separate areas. At Vanderbilt, the OR suites are on the third floor, while the cath labs are on the first floor. Orchestrating the transport of patients requiring both open-heart surgery and interventional procedures is cumbersome and often inefficient, with lag times of up to seven hours. And the need for an X-ray of the procedure would also require transporting patients from the third to the first floor. Finally, if any surgical intervention is needed after an X-ray is obtained, the patient would be transported back to the OR. Previously at Vanderbilt and still done elsewhere, physicians use what is labeled soft measurements to check a patient's recovery status. These tools include flow probes, EKGs, Echos and ultrasounds which all help determine blood flow. They are not effective when looking at the anatomy of the heart, which is vital when checking for successful grafting and other cardiac procedures, Byrne said. Another familiar scenario before the Hybrid OR - patients with aortic stenosis or a blockage of the aortic valve with blockage in the right coronary artery; they could have the right coronary artery %%%stented%%% in the cath lab and then be transported to the OR for a minimally invasive valve surgery. It required procedures in two separate locations or at two separate times - both of which require patients to leave and re-enter sterile fields. The Hybrid OR allows them both to be done at the same time, boosting patient safety. Now that Vanderbilt has opened the Hybrid OR

suites, a "one-stop shop" as Byrne refers to it, will create a new model for treating patients. "The key barrier-to-entry into this new realm has not been equipment or the space. The real barrier-to-entry is collaboration and teamwork between cardiology and cardiac surgery; not just among physicians but also among the OR team and the cath lab team. %%%Dan%%% Brinkman, RN, director of the cath lab, has been instrumental in building the team." At Vanderbilt the teams have been combined to provide a new standard of care, Byrne said. Hybrid procedures will become more common as medical centers begin to see an increase in more complex heart disease patients. The need to image results to measure outcomes will become necessary in order to be more efficient, effective and safe. "I know this is right," Byrne said, "I would want it for me or a family member. When you know it's right for the patients, you never lose. This will offer patients, families and referring physicians not only image-guided surgery, but also the ability to provide minimally invasive cardiac surgery combined with percutaneous coronary interventions." David Zhao, MD, assistant professor of Medicine and director of the cardiac catheterization lab and interventional cardiology, agrees. "First and foremost it provides better care for the patient," he said. "They receive the best of both worlds through the collaboration of interventional cardiology and cardiac surgery." Study 3: Recent research from the United States has reported on the demonstration of ubiquitin thiolester formation of UBE2Q2 (UBCi), a novel ubiquitin-conjugating enzyme with implantation site-specific expression. "We recently identified a differentially expressed gene in implantation stage rabbit endometrium encoding a new member of the ubiquitin-conjugating enzyme family designated UBE2Q2 (also known as UBCi). Its unusually high molecular mass, novel N-terminus extension, and highly selective pattern of mRNA expression suggest a specific function in implantation. "This study analyzes its relationship to the E2 ubiquitin-conjugating enzyme superfamily, investigates its enzymatic activity, and examines its localization in implantation site endometrium," wrote M.H. Meiner and colleagues, Vanderbilt University. "Construction of a dendrogram indicated that UBE2Q2 is homologous to the UBC2 family of enzymes, and isoforms are present in a broad range of species. In vitro enzymatic assays of ubiquitin thiolester formation demonstrated that UBE2Q2 is a functional ubiquitin-conjugating enzyme. "The Km for transfer of ubiquitin thiolester from E1 to UBE2Q2 is 817 nM compared to 100 nM for other E2 paralogs; this suggests that the unique amino terminal domain of UBE2Q2 confers specific functional differences," wrote the researchers. "Affinity-purified antibodies prepared with purified recombinant UBE2Q2 showed that the protein was undetectable by immunoblot analysis in endometrial lysates from estrous and Day 6 3/4 pregnant (blastocyst attachment stage) rabbits but was expressed in both mesometrial and antimesometrial implantation site endometrium of Day 8 pregnant animals. "No expression was detected in adjacent interimplantation sites. Immunohistochemistry demonstrated UBE2Q2 expression exclusively in mesometrial and antimesometrial endometrial luminal epithelial cells of the Day 8 implantation chamber," the scientists observed. "Immunohistochemical localization of ubiquitin mirrored UBE2Q2 expression, with low-to-undetectable levels in implantation sites of Day 6 3/4 pregnant endometrium but high levels in luminal epithelial cells of Day 8 pregnant endometrium," the authors noted. They concluded, "This implantation site-specific expression of UBE2Q2 in luminal epithelial cells could play major roles in orchestrating differentiation events through the modification of specific protein substrates." Meiner and colleagues published their study in Biology of Reproduction (Demonstration of ubiquitin thiolester formation of UBE2Q2 (UBCi), a novel ubiquitin-conjugating enzyme with implantation site-specific expression. Biol Reprod, 2006;75(3):395-406). For additional information, contact M.H. Meiner, Vanderbilt University, School of Medicine, Department of Obstetrics & Gynecology, Nashville, TN 37232, USA. Keywords: Nashville, Tennessee, United States, Enzymology, Female Reproductive Tract, Gynecology, Implantation, Obstetrics, Pregnancy, Ubiquitin Thiolester, Conjugating Enzymes. This article was prepared by Pharma Business Week editors from staff and other reports. Copyright 2007, Pharma Business Week via NewsRx.com & NewsRx.net.

2/7/15 (Item 6 from file: 135)

DIALOG(R)File 135:NewsRx Weekly Reports

0000501324 (THIS IS THE FULLTEXT)
Findings reported by Vanderbilt University, U.S., further disease research
Science Letter, April 17, 2007, p.3588

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 1930

TEXT: Findings reported by Vanderbilt University, U.S., further disease research. This trend article about Vanderbilt University, U.S., is an immediate alert from NewsRx to identify developing directions of research. Study 1: A new study, "Body weight and weight change in relation to blood pressure in normotensive men," is now available. According to recent research from the United States, "We examined blood pressure (BP) in association with weight change since age 20, body mass index (BMI) at different ages and fat distribution in normotensive individuals using baseline survey data collected in the Shanghai Men's Health Study, an ongoing population-based prospective cohort study of Chinese men aged 40-74 years. All anthropometric and BP measurements were performed by medical professionals." "Included in this analysis were 25 619 men who had no prior history of hypertension, diabetes or cardiovascular disease, never took any antihypertensive medication and had both normal systolic BP (SBP) and diastolic BP (DBP) (<140/90 mm Hg). Both SBP and DBP increased linearly across the whole range of weight gain since age 20. The adjusted mean differences between the highest and the lowest quintiles of weight gain were 6.0 mm Hg (95% confidence interval (CI): 5.6, 6.5) for SBP and 3.9 (95% CI: 3.6, 4.2) for DBP. When accounting for BMI at age 20, the multivariate-adjusted odds ratio of prehypertension (SBP, 120-139 and/or DBP, 80-89 mm Hg) was 4.1 (95% CI: 3.7, 4.5; P for trend <0.0001) comparing the extreme quintiles of weight gain. Similar positive associations were also observed for BMI at age 40, current BMI, circumferences of the waist and hips and waist-to-hip ratio," wrote G. Yang and colleagues, Vanderbilt University, Center for Health Services Research. The researchers concluded: "These data suggest that weight gain since age 20 and elevated adiposity may contribute significantly to the rise in BP in normotensive individuals, emphasizing the importance of weight control throughout adulthood in preventing high BP." Yang and colleagues published their study in the Journal of Human Hypertension (Body weight and weight change in relation to blood pressure in normotensive men. Journal of Human Hypertension. 2007;21(1):45-52). For additional information, contact G. Yang, Vanderbilt University School of Medicine, Dept. of Medicine, Center for Health Services Research, Vanderbilt University Medical Center, Nashville, TN 37232 USA. Study 2: Vanderbilt University Medical Center has become the first hospital in the region to offer a novel approach to cardiac surgery that includes an immediate post-operative check. Called the Hybrid OR/Cath Lab, the state-of-the-art operating suite houses all the equipment and monitoring devices necessary to perform open-heart surgeries, like coronary bypass, as well as percutaneous coronary interventions and procedures, including angioplasty and %%%stenting%%%. A major advantage will be the ability to perform an angiogram at the end of routine cardiac surgical cases to make sure grafts are in place and blood is flowing properly. Traditionally, a "before picture" was obtained prior to surgery, but an X-ray study after procedures are completed was not the standard of care. John Byrne, MD, likens the Hybrid OR to the change seen in the auto industry after the introduction of safety features like seatbelts and airbags. "We wear our seat belts every day and have air bags. How often does an air bag deploy? Maybe once or twice in your life. I for one am glad it's there when and if it does deploy. The Hybrid OR/CathLab will catch the rare but very important technical error (if it arises). Just like seat belts and air bags save your life in a car accident." Byrne, The William S. Stoney Jr. Professor of Cardiac Surgery and Chair of the Department, said most people had no idea that X-rays of cardiac surgical procedures were not performed post-surgery. He refers to the new operating environment as "sighted" cardiac surgery. "In virtually every reconstructive procedure in medicine and surgery, the medical team takes a "before" and "after" picture," said Byrne. "When we put in a central line, nasogastric tube, a

chest tube or an endotracheal tube, when your knee or hip is operated on, when you have gall bladder surgery, you get a before and after picture. When you have your heart valve operated on you have a before and after picture (intraoperative echocardiography). "But for coronary artery surgery there is no "after" picture," he said. "Placing the left internal mammary artery to the left anterior descending coronary artery is perhaps the most important reconstructive procedure any human will ever have in their entire life, yet we don't image the quality of the result. We don't measure it. We've never measured it. This has all changed at Vanderbilt." Although Vanderbilt is one of six centers nationally exploring this idea, it is believed to be the first to put the concept to use. On April 4, the first patient to undergo the newest technology was Robert Merry, a 66-year-old health care attorney from Franklin. Merry was not hesitant to become a pioneer. His triple bypass surgery was done in the new operating suite. "The first thing that interested me was the pure science of having the image done in real time," he said. "They knew that everything was OK when they closed me up. I was also excited that I was getting the A-team." Merry, who has a family history of heart disease, was pleased with the entire experience. "If anyone asked me about the Hybrid OR, I would tell them to do it. You'd want to know as much as possible about the outcome. The doctors can use these outcomes as benchmarks. Measuring outcomes is so important. This is the new direction of medicine." And what has been the delay in introducing this medical breakthrough? Byrne points to the geography of the operating room suites and the cath labs. In most hospitals these facilities are located in separate areas. At Vanderbilt, the OR suites are on the third floor, while the cath labs are on the first floor. Orchestrating the transport of patients requiring both open-heart surgery and interventional procedures is cumbersome and often inefficient, with lag times of up to seven hours. And the need for an X-ray of the procedure would also require transporting patients from the third to the first floor. Finally, if any surgical intervention is needed after an X-ray is obtained, the patient would be transported back to the OR. Previously at Vanderbilt and still done elsewhere, physicians use what is labeled soft measurements to check a patient's recovery status. These tools include flow probes, EKGs, Echos and ultrasounds which all help determine blood flow. They are not effective when looking at the anatomy of the heart, which is vital when checking for successful grafting and other cardiac procedures, Byrne said. Another familiar scenario before the Hybrid OR - patients with aortic stenosis or a blockage of the aortic valve with blockage in the right coronary artery; they could have the right coronary artery %%%stented%%% in the cath lab and then be transported to the OR for a minimally invasive valve surgery. It required procedures in two separate locations or at two separate times - both of which require patients to leave and re-enter sterile fields. The Hybrid OR allows them both to be done at the same time, boosting patient safety. Now that Vanderbilt has opened the Hybrid OR suites, a "one-stop shop" as Byrne refers to it, will create a new model for treating patients. "The key barrier-to-entry into this new realm has not been equipment or the space. The real barrier-to-entry is collaboration and teamwork between cardiology and cardiac surgery; not just among physicians but also among the OR team and the cath lab team. %%%Dan%%% Brinkman, RN, director of the cath lab, has been instrumental in building the team." At Vanderbilt the teams have been combined to provide a new standard of care, Byrne said. Hybrid procedures will become more common as medical centers begin to see an increase in more complex heart disease patients. The need to image results to measure outcomes will become necessary in order to be more efficient, effective and safe. "I know this is right," Byrne said. "I would want it for me or a family member. When you know it's right for the patients, you never lose. This will offer patients, families and referring physicians not only image-guided surgery, but also the ability to provide minimally invasive cardiac surgery combined with percutaneous coronary interventions." David Zhao, MD, assistant professor of Medicine and director of the cardiac catheterization lab and interventional cardiology, agrees. "First and foremost it provides better care for the patient," he said. "They receive the best of both worlds through the collaboration of interventional cardiology and cardiac surgery." Study 3. Recent research from the United States has reported on the demonstration of ubiquitin thiolester formation of UBE2Q2 (UBCi), a novel ubiquitin-conjugating enzyme with implantation site-specific expression. "We recently identified a differentially expressed gene in implantation stage rabbit endometrium encoding a new member of the ubiquitin-conjugating enzyme family designated UBE2Q2 (also known as UBCi). Its unusually high molecular mass, novel N-terminus extension, and highly selective pattern of mRNA expression suggest a specific function in implantation. "This study analyzes its relationship to the E2 ubiquitin-conjugating enzyme superfamily, investigates its enzymatic activity, and examines its localization in implantation site endometrium," wrote M.H. Melner and colleagues, Vanderbilt University. "Construction of a dendrogram indicated that UBE2Q2 is homologous to the UBC2 family of enzymes, and isoforms are present in a broad range of species. In vitro enzymatic assays of ubiquitin thiolester formation demonstrated that UBE2Q2 is a functional ubiquitin-conjugating enzyme. "The Km for transfer of ubiquitin thiolester from E1 to UBE2Q2 is 817 nM compared to 100 nM for other E2 paralogs; this suggests that the unique amino terminal domain of UBE2Q2 confers specific functional differences," wrote the researchers. "Affinity-purified antibodies prepared with purified recombinant UBE2Q2 showed that the protein was undetectable by immunoblot analysis in endometrial lysates from estrous and Day 6 3/4 pregnant (blastocyst attachment stage) rabbits but was expressed in both mesometrial and antimesometrial implantation site endometrium of Day 8 pregnant animals. "No expression was detected in adjacent interimplantation sites. Immunohistochemistry demonstrated UBE2Q2 expression exclusively in mesometrial and antimesometrial endometrial luminal epithelial cells of the Day 8 implantation chamber," the scientists observed. "Immunohistochemical localization of ubiquitin mirrored UBE2Q2 expression, with low-to-undetectable levels in implantation sites of Day 6 3/4 pregnant endometrium but high levels in luminal epithelial cells of Day 8 pregnant endometrium," the authors noted. They concluded, "This implantation site-specific expression of UBE2Q2 in luminal epithelial cells could play major roles in orchestrating differentiation events through the modification of specific protein substrates." Melner and colleagues published their study in

n Biology of Reproduction (Demonstration of ubiquitin thiolester formation of UBE2Q2 (UBCi), a novel ubiquitin-conjugating enzyme with implantation site-specific expression. Biol Reprod, 2006;75(3):395-406). For additional information, contact M.H. Melner, Vanderbilt University, School of Medicine, Department of Obstetrics & Gynecology, Nashville, TN 37232, USA. Keywords: Nashville, Tennessee, United States, Enzymology, Female Reproductive Tract, Gynecology, Implantation, Obstetrics, Pregnancy, Ubiquitin Thiolester, Conjugating Enzymes. This article was prepared by Science Letter editors from staff and other reports. Copyright 2007, Science Letter via NewsRx.com & NewsRx.net.

2/7/16 (Item 7 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000469851 (THIS IS THE FULLTEXT)
Research from Vanderbilt University, U.S., provides new scientific insights
Biotech Business Week, March 12, 2007, p.1573

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 1855

TEXT: Research from Vanderbilt University, U.S., provides new scientific insights.

This trend article about Vanderbilt University, U.S., is an immediate alert from NewsRx to identify developing directions of research.

Study 1: Investigators publish new data in the report "Evaluation of a digene-recommended algorithm for human papillomavirus low-positive results present in a "retest zone" " According to a study from the United States, "The Digene Hybrid Capture 2 (hc2) high-risk human papillomavirus (HPV) DNA test (Digene, Gaithersburg, MD) is widely used for triage of women with atypical squamous cells of undetermined significance, in a "retest zone" (weakly positive tests) are repeated up to 2 times according to the Digene-recommended algorithm.We studied 56 cervical samples in the retest zone."

"Specimens were tested by a multiplex polymerase chain reaction (PCR)-based genotyping assay, and relevant cytopathologic results were reviewed. Digene results were compared with a reference standard that combined PCR genotyping and cytopathology results. The first repeated Digene assay yielded a sensitivity of 85.2% and a specificity of 62.1% with false-positive and false-negative rates of 40.0% and 15.4%, respectively. The 22 negative samples underwent a second retest and 18 (82%) were negative by the reference standard," wrote K.L. Muldrew and colleagues, Vanderbilt University, Department of Pathology.

The researchers concluded, "The combined first and second retest sensitivity, specificity, and predictive values remained unchanged from the first retest alone.Repeating specimens in the retest zone is necessary, but a second retest does not offer advantages over the first retest."

Muldrew and colleagues published the results of their research in American Journal of Clinical Pathology (Evaluation of a digene-recommended algorithm for human papillomavirus low-positive results present in a "retest zone" American Journal of Clinical Pathology, 2007;127(1):97-102).

For additional information, contact K.L. Muldrew, Vanderbilt University School of Medicine, Dept. of Pathology, Nashville, TN USA.

Study 2: Vanderbilt University Medical Center has become the first hospital in the region to offer a novel approach to cardiac surgery that includes an immediate post-operative check.

Called the Hybrid OR/Cath Lab, the state-of-the-art operating suite houses all the equipment and monitoring devices necessary to perform open-heart surgeries, like coronary bypass, as well as percutaneous coronary interventions and procedures, including angioplasty and %%%stenting%%%.

A major advantage will be the ability to perform an angiogram at the end of routine cardiac surgical cases to make sure grafts are in place and blood is flowing properly. Traditionally, a "before picture" was obtained prior to surgery, but an X-ray study after procedures are completed was not the standard of care.

John Byrne, MD, likens the Hybrid OR to the change seen in the auto industry after the introduction of safety features like seatbelts and airbags.

"We wear our seat belts every day and have air bags. How often does an air bag deploy? Maybe once or twice in your life. I for one am glad it's there when and if it does deploy. The Hybrid OR/CathLab will catch the rare but very important technical error (if it arises). Just like seat belts and air bags save your life in a car accident."

Byrne, The William S. Stoney Jr. Professor of Cardiac Surgery and Chair of the Department, said most people had no idea that X-rays of cardiac surgical procedures were not performed post-surgery. He refers to the new operating environment as "lighted" cardiac surgery.

"In virtually every reconstructive procedure in medicine and surgery, the medical team takes a "before" and "after" picture," said Byrne. "When we put in a central line, nasogastric tube, a chest tube or an endotracheal tube, when your knee or hip is operated on, when you have gall bladder surgery, you get a before and after picture. When you have your heart valve operated on you have a before and after picture (intraoperative echocardiography).

"But for coronary artery surgery there is no "after" picture," he said. "Placing the left internal mammary artery to the left anterior descending coronary artery is perhaps the most important reconstructive procedure any human will ever have in their entire life, yet we don't image the quality of the result. We don't measure it. We've never measured it. This has all changed at Vanderbilt."

Although Vanderbilt is one of six centers nationally exploring this idea, it is believed to be the first to put the concept to use.

On April 4, the first patient to undergo the newest technology was Robert Metry, a 66-year-old health care attorney from Franklin.

Metry was not hesitant to become a pioneer. His triple bypass surgery was done in the new operating suite.

"The first thing that interested me was the pure science of having the image done in real time," he said. "They knew that everything was OK when they closed me up. I was also excited that I was getting the A-team."

Metry, who has a family history of heart disease, was pleased with the entire experience.

"If anyone asked me about the Hybrid OR, I would tell them to do it. You'd want to know as much as possible about the outcome. The doctors can use these outcomes as benchmarks. Measuring outcomes is so important. This is the new direction of medicine."

And what has been the delay in introducing this medical breakthrough?

Byrne points to the geography of the operating room suites and the cath labs. In most hospitals these facilities are located in separate areas. At Vanderbilt, the OR suites are on the third floor, while the cath labs are on the first floor. Orchestrating the transport of patients requiring both open-heart surgery and interventional procedures is cumbersome and often inefficient, with lag times of up to seven hours. And the need for an X-ray of the procedure would also require transporting patients from the third to the first floor. Finally, if any surgical intervention is needed after an X-ray is obtained, the patient would be transported back to the OR.

Previously at Vanderbilt and still done elsewhere, physicians use what is labeled soft measurements to check a patient's recovery status. These tools include flow probes, EKGs, Echos and ultrasounds which all help determine blood flow. They are not effective when looking at the anatomy of the heart, which is vital when checking for successful grafting and other cardiac procedures, Byrne said.

Another familiar scenario before the Hybrid OR - patients with aortic stenosis or a blockage of the aortic valve with blockage in the right coronary artery; they could have the right coronary artery %%%stented%%% in the cath lab and then be transported to the OR for a minimally invasive valve surgery. It required procedures in two separate locations or at two separate times - both of which require patients to leave and re-enter sterile fields. The Hybrid OR allows them both to be done at the same time, boosting patient safety.

Now that Vanderbilt has opened the Hybrid OR suites, a "one-stop shop" as Byrne refers to it, will create a new model for treating patients.

"The key barrier-to-entry into this new realm has not been equipment or the space. The real barrier-to-entry is collaboration and teamwork between cardiology and cardiac surgery; not just among physicians but also among the OR team and the cath lab team. %%%Dan%%% Brinkman, RN, director of the cath lab, has been instrumental in building the team."

At Vanderbilt the teams have been combined to provide a new standard of care, Byrne said. Hybrid procedures will become more common as medical centers begin to see an increase in more complex heart disease patients. The need to image results to measure outcomes will become necessary in order to be more efficient, effective and safe.

"I know this is right," Byrne said. "I would want it for me or a family member. When you know it's right for the patients, you never lose. This will offer patients, families and referring physicians not only image-guided surgery, but also the ability to provide minimally invasive cardiac surgery combined with percutaneous coronary interventions."

David Zhao, MD, assistant professor of Medicine and director of the cardiac catheterization lab and interventional cardiology, agrees.

"First and foremost it provides better care for the patient," he said. "They receive the best of both worlds through the collaboration of interventional cardiology and cardiac surgery."

Study 3: Recent research from the United States has reported on the demonstration of ubiquitin thiolester formation of UBE2Q2 (UBCI), a novel ubiquitin-conjugating enzyme with implantation site-specific expression.

"We recently identified a differentially expressed gene in implantation stage rabbit endometrium encoding a new member of the ubiquitin-conjugating enzyme family designated UBE2Q2 (also known as UBCI). Its unusually high molecular mass, novel N-terminus extension, and highly selective pattern of mRNA expression suggest a specific function in implantation.

"This study analyzee its relationship to the E2 ubiquitin-conjugating enzyme superfamily, investigates its enzymatic activity, and examines its localization in implantation site endometrium," wrote M.H. Meiner and colleagues, Vanderbilt University.

"Construction of a dendrogram indicated that UBE2Q2 is homologous to the UBC2 family of enzymes, and isoforms are present in a broad range of species. In vitro enzymatic assays of ubiquitin thiolester formation demonstrated that UBE2Q2 is a functional ubiquitin-conjugating enzyme.

"The Km for transfer of ubiquitin thiolester from E1 to UBE2Q2 is 617 nM compared to 100 nM for other E2 paralogs; this suggests that the unique amino terminal domain of UBE2Q2 confers specific functional differences," wrote the researchers.

"Affinity-purified antibodies prepared with purified recombinant UBE2Q2 showed that the protein was undetectable by immunoblot analysis in endometrial lysates from estrous and Day 6 3/4 pregnant (blastocyst attachment stage) rabbits but was expressed in both mesometrial and antimesometrial implantation site endometrium of Day 8 pregnant animals.

"No expression was detected in adjacent interimplantation sites. Immunohistochemistry demonstrated UBE2Q2 expression exclusively in mesometrial and antimesometrial endometrial luminal epithelial cells of the Day 8 implantation chamber," the scientists observed.

"Immunohistochemical localization of ubiquitin mirrored UBE2Q2 expression, with low-to-undetectable levels in implantation sites of Day 6 3/4 pregnant endometrium but high levels in luminal epithelial cells of Day 8 pregnant endometrium," the authors noted.

They concluded, "This implantation site-specific expression of UBE2Q2 in luminal epithelial cells could play major roles in orchestrating differentiation events through the modification of specific protein substrates."

Melner and colleagues published their study in Biology of Reproduction (Demonstration of ubiquitin thiolester formation of UBE2Q2 (UBCi), a novel ubiquitin-conjugating enzyme with implantation site-specific expression. Biol Reprod. 2006;75(3):395-406).

For additional information, contact M.H. Melner, Vanderbilt University, School of Medicine, Department of Obstetrics & Gynecology, Nashville, TN 37232, USA.

Keywords: Nashville, Tennessee, United States, Enzymology, Female Reproductive Tract, Gynecology, Implantation, Obstetrics, Pregnancy, Ubiquitin Thiolester, Conjugating Enzymes

This article was prepared by Biotech Business Week editors from staff and other reports. Copyright 2007, Biotech Business Week via NewsRx.com & NewsRx.net.

2/7/17 (Item 8 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000436581 (THIS IS THE FULLTEXT)
Vanderbilt University, U.S., details recent developments
Health & Medicine Week, February 5, 2007, p.4886

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 2137

TEXT: Vanderbilt University, U.S., details recent developments.

This trend article is an immediate alert from NewsRx to identify the most recent news developments at Vanderbilt University, U.S.

Report 1: A Vanderbilt researcher has discovered that some stealthy mammals have been doing something heretofore thought impossible - using the sense of smell under water.

The results of the research by Vanderbilt's Kenneth Catania, assistant professor of biology, were reported in the science journal. He became curious when he observed that a mole he was studying blew a lot of bubbles while swimming.

"This came as a total surprise because the common wisdom is that mammals can't smell underwater,' said Catania, who earlier this year won a $500,000 "genius grant" from the John D. and Catherine T. MacArthur Foundation.

"When mammals adapt to living in water, their sense of smell usually degenerates. The primary example is the cetaceans - whales and dolphins - many of which have lost their sense of smell."

Catania devised a series of experiments to determine whether the star-nosed mole and another small, semi-aquatic mammal - the water shrew - can smell objects underwater. Using a high-speed camera, he discovered how they do it.

After observing that the moles were blowing bubbles out of their nostrils and then sucking them right back in, he determined they were exhaling and inhaling the bubbles rapidly, between five and 10 times per second. That is about the same rate as the sniffing behavior of comparably sized land mammals, like rats and mice. "Rats and mice don't sniff the way we do," Catania said. "They push air 'out-in out-in' in a fashion strikingly similar to what the star-nosed mole is doing, except that it is doing it under water."

Catania mounted a high-speed video camera so that it pointed up through the bottom of a glass tank. Then he stuck various objects on the bottom of the tank - pieces of earthworm, small fish, insect cuticle and blobs of wax and silicon - and observed the moles' behavior. He saw that, when the moles approached one of these targets, they would blow bubbles that came into contact with the target's surface and then were sucked back into the nostrils.

"Because the olfactory nerves in the nose are covered with mucous, odorant molecules are all water soluble," Catania said. "So, when these bubbles come into contact with an object, it is almost inevitable that odorant molecules will mix with the air and be drawn into the nose when the bubble is inhaled."

Just because the moles are getting whiffs of interesting odors underwater doesn't necessarily mean they smell them.

So Catania devised some additional tests.

One of the complicating factors was the star-nosed mole's unusual nose, which is ringed by a star-shaped set of fleshy appendages. It uses its star like a super-sensitive set of fingers to identify objects it encounters while burrowing and swimming. So, at the same time it is sniffing at an object it is also fingering it with its star.

To determine if the mole can identify edible objects by sniffing alone, Catania created underwater scent trails leading to food and recorded how well the moles' could follow them. To keep the moles from using their tactile star, he put a grid-work between the animals and the scent trails. The openings in the grid were too small for the star appendages to squeeze through but large enough so the air bubbles could pass without difficulty.

These trials demonstrated that the moles could follow the scent trail by sniffing alone (without the tactile star). Five moles were tested on earthworm scent trails and followed the trail to its reward with accuracies ranging from 75% to 100% accuracy. Two moles were tested with fish scent trails and followed them with 85% and 100% accuracy.

When the grid was replaced with a screen with openings too small for the air bubbles to pass through, however, the moles' performance dropped down to the level of chance - the same as their performance with no-scent trails.

In order to see if this capability was limited to the star-nosed mole or if other small semi-aquatic mammals also have it, Catania captured some water shrews and began testing them. He found that they also exhibit this underwater sniffing behavior and can use it to follow underwater scent trails.

Report 2: Vanderbilt University Medical Center has become the first hospital in the region to offer a novel approach to cardiac surgery that includes an immediate post-operative check.

Called the Hybrid OR/Cath Lab, the state-of-the-art operating suite houses all the equipment and monitoring devices necessary to perform open-heart surgeries, like coronary bypass, as well as percutaneous coronary interventions and procedures, including angioplasty and %%%stenting%%%.

A major advantage will be the ability to perform an angiogram at the end of routine cardiac surgical cases to make sure grafts are in place and blood is flowing properly. Traditionally, a "before picture" was obtained prior to surgery, but an X-ray study after procedures are completed was not the standard of care.

John Byrne, MD, likens the Hybrid OR to the change seen in the auto industry after the introduction of safety features like seatbelts and airbags.

"We wear our seat belts every day and have air bags. How often does an air bag deploy? Maybe once or twice in your life. I for one am glad it's there when and if it does deploy. The Hybrid OR/CathLab will catch the rare but very important technical error (if it arises). Just like seat belts and air bags save your life in a car accident."

Byrne, The William S. Stoney Jr. Professor of Cardiac Surgery and Chair of the Department, said most people had no idea that X-rays of cardiac surgical procedures were not performed post-surgery. He refers to the new operating environment as "sighted" cardiac surgery.

"In virtually every reconstructive procedure in medicine and surgery, the medical team takes a "before" and "after" picture," said Byrne. "When we put in a central line, nasogastric tube, a chest tube or an endotracheal tube, when your knee or hip is operated on, when you have gall bladder surgery, you get a before and after picture. When you have your heart valve operated on you have a before and after picture (intraoperative echocardiography).

"But for coronary artery surgery there is no "after" picture," he said. "Placing the left internal mammary artery to the left anterior descending coronary artery is perhaps the most important reconstructive procedure any human will ever have in their entire life, yet we don't image the quality of the result. We don't measure it. We've never measured it. This has all changed at Vanderbilt."

Although Vanderbilt is one of six centers nationally exploring this idea, it is believed to be the first to put the concept to use.

On April 4, the first patient to undergo the newest technology was Robert Metry, a 66-year-old health care attorney from Franklin.

Metry was not hesitant to become a pioneer. His triple bypass surgery was done in the new operating suite.

"The first thing that interested me was the pure science of having the image done in real time," he said. "They knew that everything was OK when they closed me up. I was also excited that I was getting the A-team."

Metry, who has a family history of heart disease, was pleased with the entire experience.

"If anyone asked me about the Hybrid OR, I would tell them to do it. You'd want to know as much as possible about the outcome. The doctors can use these outcomes as benchmarks. Measuring outcomes is so important. This is the new direction of medicine."

And what has been the delay in introducing this medical breakthrough?

Byrne points to the geography of the operating room suites and the cath labs. In most hospitals these facilities are located in separate areas. At Vanderbilt, the OR suites are on the third floor, while the cath labs are on the first floor. Orchestrating the transport of patients requiring both open-heart surgery and interventional procedures is cumbersome and often inefficient, with lag times of up to seven hours. And the need for an X-ray of the procedure would also require transporting patients from the third to the first floor. Finally, if any surgical intervention is needed after an X-ray is obtained, the patient would be transported back to the OR.

Previously at Vanderbilt and still done elsewhere, physicians use what is labeled soft measurements to check a patient's recovery status. These tools include flow probes, EKGs, Echos and ultrasounds which all help determine blood flow. They are not effective when looking at the anatomy of the heart, which is vital when checking for successful grafting and other cardiac procedures, Byrne said.

Another familiar scenario before the Hybrid OR - patients with aortic stenosis or a blockage of the aortic valve with blockage in the right coronary artery; they could have the right coronary artery %%%stented%%% in the cath lab and then be transported to the OR for a minimally invasive valve surgery. It required procedures in two separate locations or at two separate times - both of which require patients to leave and re-enter sterile fields. The Hybrid OR allows them both to be done at the same time, boosting patient safety.

Now that Vanderbilt has opened the Hybrid OR suites, a "one-stop shop" as Byrne refers to it, will create a new model for treating patients.

"The key barrier-to-entry into this new realm has not been equipment or the space. The real barrier-to-entry is collaboration and teamwork between cardiology and cardiac surgery, not just among physicians but also among the OR team and the cath lab team. %%%Dan%%% Brinkman, RN, director of the cath lab, has been instrumental in building the team."

At Vanderbilt the teams have been combined to provide a new standard of care, Byrne said. Hybrid procedures will become more common as medical centers begin to see an increase in more complex heart disease patients. The need to image results to measure outcomes will become necessary in order to be more efficient, effective and safe.

"I know this is right," Byrne said. "I would want it for me or a family member. When you know it's right for the patients, you never lose. This will offer patients, families and referring physicians not only image-guided surgery, but also the ability to provide minimally invasive cardiac surgery combined with percutaneous coronary interventions."

David Zhao, MD, assistant professor of Medicine and director of the cardiac catheterization lab and interventional cardiology, agrees.

"First and foremost it provides better care for the patient," he said. "They receive the best of both worlds through the collaboration of interventional cardiology and cardiac surgery."

Report 3: The Vanderbilt-Ingram Cancer Center will participate in a major nationwide initiative to standardize proteomic technologies aimed at improving the detection and treatment of cancer.

The National Cancer Institute (NCI) announced that it will provide $35.5 million over five years to a collaborative network of "teams" to conduct Clinical Proteomic Technology Assessment for Cancer (CPTAC).

The Vanderbilt team, which will receive about $7.6 million over the five-year period, is led by Daniel C. Liebler, PhD, director of the Proteomics Laboratory in the Vanderbilt Mass Spectrometry Research Center, and director of the Jim Ayers Institute for Precancer Detection and Diagnosis.

The other centers are: the Broad Institute of MIT and Harvard; Memorial Sloan-Kettering Cancer Center; Purdue University; and the University of California, San Francisco, in collaboration with the Lawrence Berkeley National Laboratory.

"Proteomic technologies measure proteins that are found in tissues and blood," Liebler explained. "These complex mixtures of proteins are affected by the development of cancer, so the ability to detect protein combinations characteristic of disease could be a powerful means to detect cancer and monitor therapy."

Currently, however, there is a lack of standardization and reliability of techniques used to analyze proteins.

"This grant will help us move forward vital infrastructure and technology needed to evaluate key markers, ultimately use the findings to detect cancers as early as possible, choose the best course of individualized therapy and monitor the effectiveness of that therapy," said Gordon B. Mills, MD, PhD, director of the Kleberg Center for Molecular Markers at the University of Texas M. D. Anderson Cancer Center in Houston, who is collaborating with the Vanderbilt team.

This article was prepared by Health & Medicine Week editors from staff and other reports.

2/7/18 (Item 9 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports
(c) 2008 NewsRx. All rts. reserv.

0000376000 (THIS IS THE FULLTEXT)
Aberdare Ventures expands healthcare investing team
Biotech Business Week, December 4, 2006, p.241

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Consumer
WORD COUNT: 311

TEXT: Aberdare Ventures announced that Sami Hamade has joined the firm as a partner.

Hamade was most recently a VP at the Guidant Corp. where he ran the Compass Group and directed the business development teams for Guidant's three west coast businesses.

His medical device career spans 14 years - encompassing founding responsibilities at Advanced Cardiovascular Systems, directing the launch and development of several of Guidant's growth businesses such as coronary %%%stents%%% and peripheral interventions, and most recently leading Guidant's venture capital and mergers and acquisition activities. Hamade holds a bachelors degree in engineering from the American University of Beirut, a master's degree in engineering from the University of Michigan, Ann Arbor and an MBA from the Stanford Graduate School of Business.

"Aberdare's philosophy and behavior in the community represents the kind of long-term values that entrepreneurs gravitate towards. I am very happy to be part of the team and look forward to further increasing the firm's role in the medical device sector," stated Hamade.

"We are very pleased to have somebody of Sami's caliber join us. His operational and investment experiences will be of great value to Aberdare as well as the broader entrepreneurial community," added Paul Klingenstein, managing partner.

Additionally, Darren Hite has joined the firm as an associate. Hite was previously an analyst in investment banking with Robertson, Stephens & Co. He received an MBA from the Stanford Graduate School of Business and an AB degree in biology from Princeton University.

San Francisco-based Aberdare Ventures oversees more than $270 million of committed capital dedicated to investments in healthcare technology companies. Aberdare's team currently includes Managing Partner Paul Klingenstein, Partners %%%Dan%%% Kisner and Jake Odden, and Principals Vince Kim and Naheed Misfeldt.

This article was prepared by Biotech Business Week editors from staff and other reports. Copyright 2006, Biotech Business Week via NewsRx.com & NewsRx.net.

2/7/19 (Item 10 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000342903 (THIS IS THE FULLTEXT)
Hospital offers a novel approach to cardiac surgery
Cardiovascular Week, October 16, 2006, p.102

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 1239

TEXT: Vanderbilt University Medical Center has become the first hospital in the region to offer a novel approach to cardiac surgery that includes an immediate post-operative check.

Called the Hybrid OR/Cath Lab, the state-of-the-art operating suite houses all the equipment and monitoring devices necessary to perform open-heart surgeries, like coronary bypass, as well as percutaneous coronary interventions and procedures, including angioplasty and %%%stenting%%%.

A major advantage will be the ability to perform an angiogram at the end of routine cardiac surgical cases to make sure grafts are in place and blood is flowing properly. Traditionally, a "before picture" was obtained prior to surgery, but an X-ray study after procedures are completed was not the standard of care.

John Byrne, MD, likens the Hybrid OR to the change seen in the auto industry after the introduction of safety features like seatbelts and airbags.

"We wear our seat belts every day and have air bags. How often does an air bag deploy? Maybe once or twice in your life. I for one am glad it's there when and if it does deploy. The Hybrid OR/CathLab will catch the rare but very important technical error (if it arises). Just like seat belts and air bags save your life in a car accident."

Byrne, The William S. Stoney Jr. Professor of Cardiac Surgery and Chair of the Department, said most people had no idea that X-rays of cardiac surgical procedures were not performed post-surgery. He refers to the new operating environment as "sighted" cardiac surgery.

"In virtually every reconstructive procedure in medicine and surgery, the medical team takes a "before" and "after" picture," said Byrne. "When we put in a central line, nasogastric tube, a chest tube or an endotracheal tube, when your knee or hip is operated on, when you have gall bladder surgery, you get a before and after picture. When you have your heart valve operated on you have a before and after picture (intraoperative echocardiography).

"But for coronary artery surgery there is no "after" picture," he said. "Placing the left internal mammary artery to the left anterior descending coronary artery is perhaps the most important reconstructive procedure any human will ever have in their entire life, yet we don't image the quality of the result. We don't measure it. We've never measured it. This has all changed at Vanderbilt."

Although Vanderbilt is one of six centers nationally exploring this idea, it is believed to be the first to put the concept to use.

On April 4, the first patient to undergo the newest technology was Robert Metry, a 66-year-old health care attorney from Franklin.

Metry was not hesitant to become a pioneer. His triple bypass surgery was done in the new operating suite.

"The first thing that interested me was the pure science of having the image done in real time," he said. "They knew that everything was OK when they closed me up. I was also excited that I was getting the A-team."

Metry, who has a family history of heart disease, was pleased with the entire experience.

"If anyone asked me about the Hybrid OR, I would tell them to do it. You'd want to know as much as possible about the outcome. The doctors can use these outcomes as benchmarks. Measuring outcomes is so important. This is the new direction of medicine."

And what has been the delay in introducing this medical breakthrough?

Byrne points to the geography of the operating room suites and the cath labs. In most hospitals these facilities are located in separate areas. At Vanderbilt, the OR suites are on the third floor, while the cath labs are on the first floor. Orchestrating the transport of patients requiring both open-heart surgery and interventional procedures is cumbersome and often inefficient, with lag times of up to seven hours. And the need for an X-ray of the procedure would also require transporting patients from the third to the first floor. Finally, if any surgical intervention is needed after an X-ray is obtained, the patient would be transported back to the OR.

Previously at Vanderbilt and still done elsewhere, physicians use what is labeled soft measurements to check a patient's recovery status. These tools include flow probes, EKGs, Echos and ultrasounds which all help determine blood flow. They are not effective when looking at the anatomy of the heart, which is vital when checking for successful grafting and other cardiac procedures, Byrne said.

Another familiar scenario before the Hybrid OR - patients with aortic stenosis or a blockage of the aortic valve with blockage in the right coronary artery; they could have the right coronary artery %%%stented%%% in the cath lab and then be transported to the OR for a minimally invasive valve surgery. It required procedures in two separate locations or at two separate times - both of which require patients to leave and re-enter sterile fields. The Hybrid OR allows them both to be done at the same time, boosting patient safety.

Now that Vanderbilt has opened the Hybrid OR suites, a "one-stop shop" as Byrne refers to it, will create a new model for treating patients.

"The key barrier-to-entry into this new realm has not been equipment or the space. The real barrier-to-entry is collaboration and teamwork between cardiology and cardiac surgery, not just among physicians but also among the OR team and the cath lab team. %%%Dan%%% Brinkman, RN, director of the cath lab, has been instrumental in building the team."

At Vanderbilt the teams have been combined to provide a new standard of care, Byrne said. Hybrid procedures will become more common as medical centers begin to see an increase in more complex heart disease patients. The need to image results to measure outcomes will become necessary in order to be more efficient, effective and safe.

"I know this is right," Byrne said. "I would want it for me or a family member. When you know it's right for the patients, you never lose. This will offer patients, families and referring physicians not only image-guided surgery, but also the ability to provide minimally invasive cardiac surgery combined with percutaneous coronary interventions."

David Zhao, MD, assistant professor of Medicine and director of the cardiac catheterization lab and interventional cardiology, agrees.

"First and foremost it provides better care for the patient," he said. "They receive the best of both worlds through the collaboration of interventional cardiology and cardiac surgery."

Zhao lauds the new technology, stating that the use of angiography has already proven worthwhile. During a recent bypass, the "after" picture was able to show surgeons that the clip, placed on the graft to stop bleeding, was actually too close to the artery, which comprised the graft and could potentially harm the patient's health.

"The mammary artery has a lot of branches and is the only revascularization conduit that prolongs life," Zhao said. "In time, that graft would have become occluded and it would not have been discovered for

several months or even years if it was not for the Hybrid OR. By doing the post-bypass angiography, you are 100% sure the patient has perfect grafts."

This article was prepared by Cardiovascular Week editors from staff and other reports. Copyright 2006, Cardiovascular Week via NewsRx.com & NewsRx.net.

2/7/20 (Item 11 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000220550 (THIS IS THE FULLTEXT)
Hospitals adopting data management to analyze spending information
Biotech Business Week, June 6, 2005, p.292

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Consumer
WORD COUNT: 1035

TEXT: Hospitals across the country are increasingly adopting the data management and maintenance services provided by Neoforma, Inc. (NEOF) to analyze spending information and reduce supply chain costs.

Many hospitals that belong to VHA Inc., the national healthcare alliance, are using Neoforma Data Management Solution (Neoforma DMS) and realizing increased efficiencies and savings opportunities from improved visibility to clean, standardized supply chain data, which enables more powerful, ongoing spend analyses across a hospital's total purchasing history.

"Information is power, and Neoforma DMS gave us access to data that allowed us to perform analyses across our system in a way that wasn't possible before because the condition of our data wouldn't allow it," says Jack Medkeff, director of materials services for Genesis Healthcare System in Zanesville, Ohio.

Medkeff, a 30-year veteran of the healthcare supply chain, recently completed a Neoforma DMS project that generated more than $400,000 in immediate savings opportunities for Genesis, simply by pointing out where the hospital was purchasing products with off-contract prices across their purchase order history.

Neoforma DMS's comprehensive supplier-provided database has more than two million records of accurate vendor and product information and sophisticated auto-matching technology that accelerated the cleaning and normalization of Genesis' item master. Genesis was able to reduce the number of records in its item master by nearly 30% by eliminating erroneous and duplicate entries, as well as those items that had not been purchased for years.

From there, using industry-leading loading technology, Neoforma's team of healthcare professionals quickly categorized Genesis' item master to the UNSPSC product classification system. With the help of Neoforma DMS and Neoforma supply chain experts, Genesis was able to quickly get to immediate savings opportunities across its entire supply spend.

"Neoforma understands what I need to alleviate cost pressures my hospitals face, and its provider focus translates to real hard dollar savings. Because of this, and their partnership with VHA, Neoforma is the only one I trust to provide sensitive pricing data to help drive decisions," Medkeff stated.

Medkeff continued, "Without changing a single process today, Neoforma pointed out where I could save my hospital nearly half-a-million dollars, money better spent on important patient care initiatives."

To promote greater awareness of supply spending patterns across its organization, 551-bed University Healthcare System in Augusta, Georgia, worked with the Neoforma DMS team to use the UNSPSC code to correctly classify 10,000 individual products in the hospital's item master. Accuracy is key to performing the kind of insightful analyses University needed to lock in the most advantageous prices for the innovative products used at the hospital, such as drug-eluting %%%stents%%% and neurosurgical implants.

Neoforma DMS revealed opportunities for the hospital to enhance its bargaining power with manufacturers, and enabled the hospital, in one case, to negotiate a greater manufacturer market share contract for drug-eluting %%%stents%%%, reducing costs by 14% - a savings of $600,000 per year.

"My reports to the administration now contain month-to-month spending levels, so there is a greater awareness of spending patterns and priorities at the executive level," says Mike Brown, University's director of purchasing. "We're also better able to phase out discontinued products and get new products coded in a timelier manner. Neoforma is the link between my data and the ability to drive decisions that made all of this possible."

Brown, a supply chain management expert who entered healthcare from manufacturing 2 years ago, was also impressed with the institutional knowledge and provider focus of the Neoforma DMS team, attributes he says are critical when looking for a supply chain partner.

Although South Jersey Healthcare Regional Medical Center, in Vineland, New Jersey, was one of the newest hospitals in the state, its item master and operating room (OR) files were outdated and inaccurate. Much of the organization's supply information was more than a decade old.

"We had a database made up of about 40,000 records, and many had the deficiencies you'd expect to see with an antiquated system: duplicate and erroneous entries, pricing issues, cryptic descriptions and information gaps," says Bob Minnick, director of materials management for the 262-bed hospital.

After completing a Neoforma DMS implementation as part of an upgrade to its new materials system late last year, the hospital was finally able to generate insightful reports that helped to identify volume aggregation opportunities in its OR, and to take advantage of the hospital's strategic cost savings programs. Achieving synchronized and accurate data in its OR and item master files had positive implications across South Jersey's organization.

"Neoforma is a trusted partner in VHA's supply chain management initiatives. Neoforma has shown again and again that its solutions drive measurable value to our members," says Mike Cummins, chief information office for VHA.

"With its leading-edge technology and support for industry standards, Neoforma DMS is a proven solution for driving additional efficiencies and uncovering cost savings opportunities in the supply chain. It is the perfect complement to the portfolio of supply chain services already available to VHA members through Neoforma," continued Cummins.

In June 2004, VHA named Neoforma as a provider of supply chain data cleansing and maintenance services to the VHA membership base.

"Clean, accurate data is the foundation for a more efficient healthcare supply chain," says %%%Dan%%% Eckert, Neoforma president and chief operating officer. "We believe that information can provide our customers the power they need to drive change, through improved decision making. The results improve the bottom line for the hospital and support the critical mission of the hospital - taking care of the patient."

Neoforma DMS is a powerful data cleansing and maintenance solution that enables hospital customers to improve the accuracy of their item master and vendor master data files, as well as increase utilization through contract matching services. Additionally, Neoforma DMS offers rich intelligence on spend data and purchasing history so that hospitals have accurate information to make better decisions on supply spend.

Neoforma is a supply chain management solutions provider for the healthcare industry.

This article was prepared by Biotech Business Week editors from staff and other reports. Copyright 2005, Biotech Business Week via NewsRx.com & NewsRx.net.

2/7/21 (Item 12 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000097090 (THIS IS THE FULLTEXT)
Popularity of new drug-coated %%%stents%%% exceeds supply
Biotech Week, July 23, 2003, p.160

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Consumer
WORD COUNT: 808

TEXT: Barely 2 months after Johnson & Johnson's new drug-coated %%%stents%%% hit the U.S. market, demand from patients and doctors has greatly eclipsed supply. The %%%stents%%% reduce chances a heart artery will reclog after being cleared out and propped open.

Hospitals have been complaining about the shortage to Cordis Corp., the unit of New Brunswick, N.J.-based Johnson & Johnson that makes %%%stents%%%, and Cordis has increased manufacturing capacity about 50%, Sam Liang, vice president of the global %%%stent%%% business at Cordis in Miami Lakes, Florida, said.

He predicts Cordis by September will have adequate supply of the new "Cypher" %%%stents%%%, tiny metal scaffolds that slowly release medicine to prevent scarring around the %%%stent%%% from reclogging an artery cleared out by angioplasty. That forces roughly 15% of patients with bare metal %%%stents%%% to undergo another artery-clearing procedure within a year; with Cypher, the rate is about 4%, Cordis says.

"This is a substantial breakthrough," said American Heart Association spokesman Dr. Donald LaVan, a cardiologist at the University of Pennsylvania School of Medicine. "I have a hunch in the long run that's all we're going to be using."

Fueled by patient demand, doctors' enthusiasm and use in sicker patients than expected, Cordis' share of the U.S. %%%stent%%% market jumped from 30% to more than 60% within 5 weeks of Cypher's April 24 approval, Liang said.

Dr. Mark Porway, an interventional cardiologist at Morristown Memorial Hospital, said his hospital gets about 4 dozen Cyphers each Monday and often runs out.

"Right now, there are shortages in every hospital in the country," he said. "Virtually every patient who comes to see me who is in anyway knowledgeable asks for it."

Robert Wood Johnson University Hospital in New Brunswick already has 35 people on a waiting list.

"People who can't wait are having a bare %%%stent%%% put in and others whose condition is stable enough to wait can have a Cypher %%%stent%%% reserved for them," said hospital spokesman John Patella.

There have been other problems.

U.S. Food and Drug Administration spokeswoman Kathleen Quinn said the agency is looking into the deaths of two patients at St. Francis Hospital in Roslyn, New York, after they developed blood clots around Cypher %%%stents%%%.

The hospital said incidence of clot formation in the 264 patients it has given Cypher %%%stents%%% appears similar to the rate with bare metal %%%stents%%%. Hospital spokesman Andy Kraus would give no further information.

Liang said the patients were elderly and extremely sick, and the problem was not with the %%%stent%%%.

%%%Stents%%% have been used since 1987 to prevent gradual buildup of plaque from again narrowing a just-cleared artery, a condition called restenosis that occurred in about 25% of patients. %%%Stents%%% cut the need for a repeat procedure by nearly half, and Cypher cut it much further.

For the first several weeks after implantation - when scar tissue is most likely to form - it steadily releases into the artery wall the drug sirolimus, which reduces inflammation and limits immune cell production there. Cordis has an exclusive license to use the drug from Wyeth, which sells it as Rapamune to prevent organ transplant rejection.

Cypher isn't right for every patient, said Dr. Spencer King, director of interventional cardiology at Piedmont Hospital and a professor of medicine at Emory University in Atlanta. He said unless patients have diabetes, narrow arteries or a long clogged stretch, bare metal %%%stents%%% are generally fine.

"Restenosis, as far as we know, doesn't alter your survival," Kings said, but many physicians feel they should use a Cypher so patients won't think the hospital was trying to save money.

Cypher %%%stents%%% retail for $3195, compared to about $1000 for bare metal ones, and while Medicare is paying nearly all of the cost, hospitals are losing some money on Cyphers, doctors say.

For now, Cordis has the drug-coated %%%stent%%% market to itself, but Boston Scientific likely will get its version approved early next year, said %%%Dan%%% Lemaitre, medical technology analyst at Merrill Lynch.

He predicted U.S. %%%stent%%% procedures will jump from about 1.7 million last year to 2.6 million in 2006 - and revenues will grow from $2.4 billion to more than $7.5 billion over that span. That's because of the higher price and Cypher's popularity boosting the number of angioplasties and drawing patients who previously would have gotten bypass surgery.

Lemaitre expects sales of bare metal %%%stents%%% at one Cordis competitor to drop 75% by next year.

Meanwhile, Liang said Cordis hopes to soon have approval for Cypher %%%stents%%% in very narrow and very large diameters - its current selection suits only about 80% of patients - and it plans to launch to more advanced versions of Cypher over the next couple years.

This article was prepared by Biotech Week editors from staff and other reports.

2/7/22 (Item 13 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000064575 (THIS IS THE FULLTEXT)
Patent filed for new angiogenesis %%%stent%%%
Angiogenesis Weekly, August 2, 2002, p.11

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Consumer
WORD COUNT: 395

TEXT: Endovasc, Ltd., Inc., (ENDV; ED7) announced the filing of a patent application for a novel method for stimulating growth of new blood vessels in the heart and limbs by releasing therapeutic amounts of its new drug Angiogenix (a nicotine acetylcholine receptor agonist) from a %%%stent%%% leading to an ischemic (blood starved) area by the heart or limbs.

According to the company, the %%%stent%%% will be used as the delivery platform which is first used to open the vessel while its new drug Angiogenix stimulates new circulation by causing new blood vessels to grow into the tissue in order to supply fresh blood, oxygen and nutrients.

According to Endovasc Vice President of Research and Development Diane Dottavio, "We have submitted an abstract on our discovery to a major heart conference that describes our process in detail, but suffice to say at this time, %%%stents%%% may provide a much safer and effective method of releasing drugs that stimulate the angiogenesis, or the growth of new blood vessels. Though our results with endocardial catheters have effectively demonstrated the efficacy of intracatheter needle injection in the heart, the technique requires considerable skill and some very expensive equipment. %%%Stents%%% are obviously commonly used all over the world by medical practitioners who have developed a familiarity with them that has not caught up with the catheters, needles, and equipment used currently."

Endovasc estimates that the current market potential for its Angiogenix %%%stents%%% is approximately $1 billion per year. David P. Summers, chairman and CEO said, "We made a choice to establish a joint venture with MIV Therapeutics primarily because they chose our PROStent therapeutic as a coating for preventing restenosis, and our PROStent coating process is cross-transferable to Angiogenix coatings. They also have a superior %%%stent%%% and manufacturing capability that will speed up the development."

Alan Lindsay, MIV Therapeutics chairman and CEO said, "This Angiogenix coating on %%%stents%%% is believed to be breakthrough technology as it has the potential to stimulate the growth of new blood vessels in the heart, thus revitalizing the heart. We as a company are excited to be involved with Endovasc in the research and development of this leading edge technology."

The company said it had plans to test the concept at Columbia University in %%%Dan%%% Burkhoff's laboratory this fall.

This article was prepared by Angiogenesis Weekly editors from staff and other reports.

2/7/23 (Item 1 from file: 144)

DIALOG(R)File 144:Pascal
(c) 2006 INIST/CNRS. All rts. reserv.

17922542 PASCAL No.: 06-0524280
Transfection of the %%%DAN%%% for the receptor KDR/flk-1 attenuates neointimal proliferation and luminal narrowing in a coronary %%%stent%%% angioplasty model
BUCHWALD Arnd B; KUNZE Christopher; WALTENBERGER Johannes; UNTERBERG-BUCHWALD Christina
Staedtisches Krankenhaus Kiel, I. Medizinische Klinik, Kiel, Germany; Department of Pediatric Cardiology, University of Gottingen, Gottingen, Germany; Department of Cardiology, University Hospital, Maastricht, Netherlands; Department of Cardiology, University of Gottingen, Gottingen, Germany
Journal: The Journal of surgical research, 2006, 136 (1) 120-124
ISSN: 0022-4804 CODEN: JSGRA2 Availability: INIST-9554; 354000158869150190
No. of Refs.: 30 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United States
Language: English
Background. Neointimal proliferation resulting in luminal renarrowing is the major cause of restenosis limiting the long-term success of coronary angioplasty in 20 to 30% of patients. Local transfection of the DNA encoding for VEGF has been shown to enhance re-endothelialization and reduce neointimal proliferation in an experimental model. We tested the hypothesis that transfection of the DNA for the receptor of vascular endothelial growth factor VEGF, KDR/flk-1, reduces neointimal proliferation after angioplasty. Methods. In a minipig model, we performed coronary %%%stent%%% implantation, followed by injection of either KDR/flk-1 DNA (200 mu g of linearized DNA in a CMV-promotor) or LacZ control in two coronary artery segments per animal in a randomized, blinded protocol (n = 22 animals). Expression of KDR/flk-1 was analyzed using in situ hybridization after 4, 7, and 14 days. Results. In KDR-transfected coronary segments, expression of KDR/flk-1 occurred earlier and to much stronger extent compared to LacZ-transfected segments. After 4 weeks (n = 10) neointimal proliferation and luminal narrowing was significantly reduced in KDR/flk-1 transfected animals. No expression of locally transfected DNA was detected in other organs. Conclusion. The hypothesis is supported, that expression of the VEGF-receptor KDR/flk-1 can be rate-limiting for endothelial regeneration and that its transient overexpression at the time angioplasty can prevent excessive neointimal proliferation resulting in restenosis.

2/7/24 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal
(c) 2008 INIST/CNRS. All rts. reserv.

16014180 PASCAL No.: 03-0160109
Balloon surface changes after %%%stent%%% deployment: Influence of the crimping technique
RONDEAU F; PILET P; HEYMANN D; CROCHET D; GRIMANDI G
Central Pharmacy, University Hospital, 44093 Nantes, France; Center for Electronic Microscopy, University Hospital, 44093 Nantes, France; EE 9901 Laboratory, College of Medicine, University of Nantes, 44093 Nantes, France ; Hemodynamics Centre, University Hospital, 44093 Nantes, France
Journal: ITBM REMI, 2002, 23 (6) 357-362
ISSN: 1297-9562 Availability: INIST-18473; 354000105653240060
No. of Refs.: 6 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: France
Language: English Summary Language: French
L'implantation d'une endoprothese coronaire est de plus en plus frequente au cours d'une angioplastie transluminale percutanee (ACTP). L'evolution des dispositifs medicaux a privilegie le sertissage industriel au sertissage manuel. Cette etude se propose de comparer les effets de deux types sertissage sur la surface de ballonnets apres largage. Trois groupes de catheters ont ete constitues et etudies apres la procedure de ACTP: un groupe controle (n = 30) catheters utilises pour une angioplastie sans endoprothese (Pronto Rely , et Viva); un groupe avec sertissage manuel de l'endoprothese (n = 30: Power Grip /Palmaz Schatz , Viva / Nir) et un groupe avec un sertissage industriel (n = 50; Power Grip /Palmaz Schatz , Multi Link , LTX /GFX 2). Les surfaces des ballonnets ont ete observees au microscope electronique a balayage (MEB) et les pressions d'eclatement ont ete mesurees a l'aide d'un manometre. Les observations au MEB indiquent que la surface de tous les ballonnets ayant largue une endoprothese est alteree, ce qui n'est pas observe dans le groupe controle. Les traumatismes recouvrent moins de 5% de la surface des ballonnets du groupe sertissage industriel et plus de 20% de leur surface %%%dan%%% le groupe sertissage manuel. En revanche aucune difference de pression d'eclatement a ete observee. Ces resultats suggerent que le sertissage industriel est moins traumatisant que le sertissage manuel. Dans tous les cas, les observations au MEB indiquent qu'il est fortement deconseille d'effectuer un essai de mobilisation sur une endoprothese sertie manuellement.

2/7/25 (Item 3 from file: 144)
DIALOG(R)File 144:Pascal
(c) 2008 INIST/CNRS. All rts. reserv.

15082866 PASCAL No.: 01-0242469
Traitement par %%%stents%%% aorto-iliaques d'une ischemie aigue du membre inferieur compliquant une dissection aortique aigue type B
(Treatment with aorto iliac endoprosthesis of lower limb ischemia in a patient with acute type B dissection)
CHAHID T; MIGUEL B; MORID R; RAVEL A; GARCIER J M; CAMILLERI L; BOYER L
Service de Radiologie (Pr Viallet), Hopital G Montpied, 30, place Henri Dunand - BP 69, 63003 Clermont Ferrand, France; Service de Chirurgie Cardio-Vasculaire (Pr de Riberolles), Hopital G Montpied, 30, place Henri Dunand - BP 69, 63003 Clermont Ferrand, France
Journal: Journal de radiologie (Paris), 2001, 82 (4) 506-509
ISSN: 0221-0363 CODEN: JORADF Availability: INIST-427; 354000097647060120
No. of Refs.: 20 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: France
Language: French Summary Language: English
Le traitement par %%%stents%%% aorto-iliaques d'une ischemie aigue du membre inferieur droit compliquant l'installation brutal d'une dissection type B est rapporte. Cette ischemie dynamique (ischemie distale liee a l'obstruction du vrai chenal aorti que, sans extension de la dissection dans cette artere iliaque) a pu etre traitee avec un bon resultat par la mise en plan d'une endoprothese non couverte. Le deplacement du flap apres %%%stenting%%% iliaque droit creant une ischemie relative ai niveau de l'axe iliaque gauche, un %%%stent%%% a egalement ete mis en place de ce cote. Un elargissement progressif du perimetre de marche pour atteindre 1 500 metres apres huit mois a ete enuite observe. La place des techniques percutanees %%%dan%%% la prise en charge des complications ischemiques viscerales ou des membres inferieurs au cours de dissections aortique est discutee.

2/7/26 (Item 1 from file: 266)
DIALOG(R)File 266:FEDRIP
Comp & dist by NTIS, Intl Copyright All Rights Res. All rts. reserv.

00643238
IDENTIFYING NO.: 5R01HL030946-24 AGENCY CODE: CRISP
Mechanisms of Arterial Graft Healing
PRINCIPAL INVESTIGATOR: CLOWES, ALEXANDER W
ADDRESS: CLOWES@U.WASHINGTON.EDU UNIVERSITY OF WASHINGTON 1959 NEPACIFIC STREET SEATTLE, WA 98105
PERFORMING ORG.: UNIVERSITY OF WASHINGTON, SEATTLE, WASHINGTON

SPONSORING ORG.: NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
DATES: 2007/01/83 TO 2006/30/10 FY: 2007 TYPE OF AWARD: Noncompeting Continuation (Type 5)
SUMMARY: DESCRIPTION (provided by applicant): Approximately 30% of vascular interventions using grafts and %%%stents%%% to correct the problems associated with atherosclerosis fail largely as a result of intimal hyperplasia resulting from smooth muscle cell (SMC) growth and wall thickening. While most research has been directed at preventing wall thickening, an alternative might be to stimulate neointimal atrophy after lumenal narrowing has developed. We have demonstrated that high blood flow induces neointimal atrophy in baboon PTFE grafts, but not in the normal iliac artery. We have also found that bone morphogenetic protein (BMP}-4 is induced by high blood flow, while the. BMP inhibitor %%%noggin%%% is suppressed. We propose to test the hypothesis that neointimal atrophy requires a loss of wall tension in the presence of inflammation by comparing loose and tight PTFE wraps around the baboon artery with high blood flow. We will use subtractive suppressive hybridization with DMA microarrays to identify a short list of genes that are regulated during atrophy of both graft neointima and artery and will then determine whether these genes are expressed (or repressed) in the thinning fibrous cap of stenotic atherosclerotic human carotid arteries. We will determine whether baboon neointimal atrophy involves the loss of specific matrix molecules (especially versican) by quantitating glycosaminoglycans using fluorophore assisted carbohydrate electrophoresis. Finally, we will test the hypothesis that an established neointima can be induced pharmacologically to atrophy by overexpressing BMP-4 in the face of normal blood flow. In addition, we will test whether overexpressing %%%noggin%%% blocks high blood flow-mediated neointimal atrophy.

2/7/27 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0346353 DBR Accession No.: 2004-18645 PATENT
New pharmaceutical composition comprising a bone morphogenic protein antagonist, useful for treating vascular inflammation or atherosclerosis - modified protein and expression vector for use in disease therapy
AUTHOR: JO H
PATENT ASSIGNEE: GEORGIA TECH RES CORP 2004
PATENT NUMBER: WO 200462621 PATENT DATE: 20040729 WPI ACCESSION NO.: 2004-544035 (200452)
PRIORITY APPLIC. NO.: US 439667 APPLIC. DATE: 20030113
NATIONAL APPLIC. NO.: WO 2004US759 APPLIC. DATE: 20040113
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A pharmaceutical composition comprising a bone morphogenic protein antagonist or its prodrug in an amount for inhibiting or reducing vascular inflammation by interfering with binding of bone morphogenic protein or its fragment to bone morphogenic protein receptors, is new. DETAILED DESCRIPTION - A pharmaceutical composition comprising a bone morphogenic protein antagonist or its prodrug in an amount for inhibiting or reducing vascular inflammation by interfering with binding of bone morphogenic protein or its fragment to bone morphogenic protein receptors, where the antagonist includes at least a portion of any of the polypeptide: Cys-Xaa-Cys-Xaa-Gly-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa; Cys-Xaa-Cys-Xa a-Cys-Xaa-Gly-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa; Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys; Cys-Xaa-Cys-Xaa-Cy s-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Cys-Xaa-Cys; Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys-Xaa-Cys (SEQ ID NOS: 6-10). INDEPENDENT CLAIMS are also included for: (1) a vector comprising a promoter operably linked to polynucleotide encoding a modified bone morphogenic polypeptide that binds to a bone morphogenic protein receptor without activating the receptor; (2) a medical device comprising a bone morphogenic protein antagonist, bone morphogenic protein receptor antagonist, or a combination; (3) a method of decreasing or inhibiting monocyte adhesion to vascular cells; (4) a method of inhibiting a vascular inflammatory response; (5) a method of inhibiting a vascular inflammation; and (6) a method for treating vascular inflammation or atherosclerosis. BIOTECHNOLOGY - Preferred Composition: Specifically, the pharmaceutical composition comprises a modified morphogenic polypeptide or its prodrug in an amount for inhibiting vascular inflammation by competitively inhibiting binding of bone morphogenic protein to endothelial bone morphogenic protein receptors, where binding of the modified bone morphogenic protein to bone morphogenic protein receptor does not activate the receptor. The bone morphogenic protein receptors are vascular cell bone morphogenic protein receptors. The bone morphogenic protein antagonist comprises a polypeptide %%%noggin%%%, or N-terminal fragment of %%%noggin%%%, %%%chordin%%%, %%%DAN%%%, or %%%veinless%%%. The bone morphogenic protein is bone morphogenic protein 4. The composition further comprises a second therapeutic agent, e.g. antiinflammatory agent, cholesterol lowering agent, or a combination. The composition further comprises a pharmaceutical carrier. Preferred Vector: The promoter is an inducible promoter. The promoter is induced in vascular cells, i.e. endothelial cells. Preferred Medical Device: The device is a vascular %%%stent%%%. The device releases an amount of antagonist to inhibit or reduce vascular inflammation by inferring with or reducing the binding of bone morphogenic protein or its fragment to a bone morphogenic protein receptor. The device is configured to be inserted into a blood vessel. The release of antagonist is sustained over a period of time. Preferred Method: Decreasing or inhibiting monocyte adhesion to vascular cells comprises inhibiting binding of bone morphogenic polypeptide to the vascular cells by contacting bone morphogenic polypeptide present in vascular fluid or tissue in contact with vascular cells with a bone morphogenic polypeptide antagonist in an amount to inhibit or educe the expression of cell adhesion molecules by the vascular cells. Inhibiting a vascular inflammatory response comprises contacting extracellular vascular fluid with an amount of bone morphogenic protein antagonist to inhibit binding of bone morphogenic protein to vascular cells in contact with the vascular fluid. Inhibiting a vascular inflammation comprises contacting vascular cells with a bone morphogenic protein antagonist in an amount to inhibit or reduce binding of bone morphogenic protein to the vascular cells. Alternatively, the method comprises contacting vascular cells with an inhibitory polynucleotide specific for a bone morphogenic polypeptide or bone morphogenic protein receptor. Treating vascular inflammation or atherosclerosis comprises administering to a host an amount of bone morphogenic protein antagonist or bone morphogenic protein receptor antagonist to inhibit binding of bone morphogenic protein or its fragment to vascular cells of the host and inhibit or reduce the expression of cell surface adhesion polypeptides. The binding of bone morphogenic protein to bone morphogenic protein receptors is reduced or inhibited. Alternatively, the method comprises inserting the medical device of (2) into a vascular conduit of a host. ACTIVITY - Vasotropic; Antiinflammatory; Antiarteriosclerotic. No biological data given. MECHANISM OF ACTION - Bone morphogenic protein antagonist. USE - The pharmaceutical composition, medical device, and methods are useful for treating vascular inflammation or atherosclerosis. ADMINISTRATION - Dosage is 1-100 mg/kg, preferably 10-20 mg/kg, by buccal, rectal, vaginal, topical, nasal, parenteral, paracanceral, transmucosal, transdermal, intramuscular, intravenous, intradermal, subcutaneous, intraperitoneal, intraventricular, intracranial, or intratumor means. EXAMPLE - No relevant example given.(91 pages)

2/7/28 (Item 1 from file: 370)
DIALOG(R)File 370:Science

00508128 (USE 9 FOR FULLTEXT)
Synaptic Segregation at the Developing Neuromuscular Junction
Gan, Wen-Biao; Lichtman, Jeff W.
Department of Anatomy and Neurobiology, Washington University School of Medicine, 660 South Euclid Avenue, Box 8108, St. Louis, MO 63110, USA.
Science Vol. 282 5393 pp. 1508
Publication Date: 11-20-1998 (981120) Publication Year: 1998
Document Type: Journal ISSN: 0036-8075

Language: English
Section Heading: Reports
Word Count: 2283

Abstract: Throughout the developing nervous system, competition between axons causes the permanent removal of some synaptic connections. In mouse neuromuscular junctions at birth, terminal branches of different axons are intermingled. However, during the several weeks after birth, these branches progressively segregated into nonoverlapping compartments before the complete withdrawal of all but one axon. Segregation was caused by selective branch atrophy, detachment, and withdrawal; the axon branches that were nearest to the competitor's branches were removed before the more distant branches were removed. This progression suggests that the signals that mediate the competitive removal of synapses must decrease in potency over short distances.

References and Notes:

1. Purves, D., Lichtman, J. W., Principles of Neural Development, 1985, Sinauer, Sunderland, MA, ; ;
2. Redfern, P. A., J. Physiol., 209 1970, 701 Jansen, J. K. S., Riadby, T., Prog. Neurobiol., 34 1990, 39 ;
3. Gan, W.-B., Macagno, E. R., J. Neurosci., 15 1995, 3243 ;
4. Neonatal mice (between P0 and P17) were anesthetized with 0.1 ml of sodium pentobarbital. Sternomastoid muscles were then dissected and placed in petri dishes in physiological saline. In some cases, junctional AChRs were labeled for 10 min with tetramethyl rhodamine-conjugated a-bungarotoxin (5 (mu) g/ml) (Molecular Probes, Eugene, OR). Sharp electrodes (5 to 10 megohms, as measured with 3 M KCl) were backfilled with a 1% solution of 3,3 (prime) -dioctadecyloxacarbocyanine perchlorate (DiO) (Molecular Probes) in a 100% solution of methylene chloride (Sigma) and positioned on a superficial neuromuscular junction. Depolarizing current (200 ms, 1 to 10 nA, and 1 Hz) was applied for a few seconds until a dye crystal was deposited at the junction. The muscle was then fixed in a 4% solution of paraformaldehyde for 12 hours, over which time the fluorescent DiO lipid labeled many terminals of one motor unit that were distributed over several hundred micrometers. For the labeling of two competing axons at the same neuromuscular junction, two electrodes [each containing 1% solutions of either 1,1 (prime) -dioctadecyl-3,3,3 (prime) ,3 (prime) -tetramethylindocarbocyanine perchlorate (DiI) (Molecular Probes) or DiO in a 100% solution of methylene chloride] were used to deposit dye. In this way, two different subsets of axon terminals, which by chance occasionally converged at the same junction, were labeled. All labeled junctions were imaged with confocal microscopy (Noran Oz Odyssey, Olympus Fluoview, and Bio-Rad MRC1024) with 1.4-numerical aperture objectives, and three-dimensional (3D) reconstructions were generated with the Bio-Rad MRC1024 software. ;
5. Balice-Gordon, R. J., Lichtman, J. W., J. Neurosci., 13 1993, 834 ;
6. Staining of all motor axons [with antibodies against neurofilaments, synaptic vesicles (SV2), and acetylated microtubules] was done similarly as described in (B11) . For tetanus toxin labeling, the preparation was incubated with a fluorescein isothiocyanate-conjugated recombinant tetanus toxin C fragment (Boehringer Mannheim) for 20 min (1:10 dilution); ;
7. Balice-Gordon, R. J., Chua, C. K., Nelson, C. C., Lichtman, J. W., Neuron, 11 1993, 801 ;
8. To measure the separation of two competing axons, we calculated a segregation index as the distance between centroids of the competing axons divided by the total length of the junction, which was measured along a line passing through the two centroids. The centroid (geometric center) of the terminal branches of each competing axon was obtained with IP Lab software (Scanalytics, Fairfax, VA). The particular shape of the junction will influence this measure to some degree. For hemicircles that approximate the shapes of competing axon terminals, values >0.39 indicate that the regions are completely segregated. ;
9. Because of the low incidence of multiply innervated junctions after P12, we used antibody staining instead of lipophilic dyes to label competing axons at P16-17. Competing axons innervating the same junction at this age were traced several hundred micrometers back into nerve bundles to confirm that they were separate axons. ;
10. Riley, D. A., Brain Res., 134 1977, 279 ; J. Neurocytol. 10, 425 (1981). ;
11. Colman, H., Nabekura, J., Lichtman, J. W., Science, 275 1997, 356 ;
12. %%%Stent%%%, G. S., Proc. Natl. Acad. Sci. U.S.A., 70 1973, 997 ;
13. Balice-Gordon, R. J., Lichtman, J. W., Nature, 372 1994, 519 ; C. Jennings, ibid., p. 498. ;
14. Lo, Y.-J., Poo, M.-M., Science, 254, 1991, 1019 %%%Dan%%%, Y., Poo, M.-M., ibid., 256, 1992, 1570 Cash, S., %%%Dan%%%, Y., Poo, M.-M., Zucker, R., Neuron, 16, 1996, 745 ;
15. Rotzler, S., Schramek, H., Brenner, H. R., Nature, 349, 1991, 337 ;
16. Zou, D. J., Cline, H. T., Neuron, 16, 1996, 529 Wu, G.-Y., Malinow, R., Cline, H. T., Science, 274, 1996, 972 ;
17. Brown, M. C., Jansen, J. K. S., Van Essen, D., J. Physiol., 261 1976, 387 Kuffler, D., Thompson, W., Jansen, J. K. S., Brain Res., 138 1977, 353 ;
18. Hubel, D. H., Wiesel, T. N., LeVay, S., Philos. Trans. R. Soc. London Ser. B, 278 1977, 377 Purves, D., Lichtman, J. W., Science, 210 1980, 153 Crair, M. C., Gillespie, D. C., Stryker, M. P., ibid., 279, 1998, 566 ; A. A. Penn, P. A. Riquelme, M. B. Feller, C. J. Shatz, ibid., p. 2108. ;
19. Forehand, C. J., Purves, D., J. Neurosci., 4 1984, 1 Young, R., Rubel, E. W., J. Comp. Neurol., 254, 1986, 425 Bank, M., Schacher, S., J. Neurosci., 12 1992, 2960 Bravin, M., Rossi, F., Strata, P., J. Comp. Neurol., 357 1995, 395 ;
20. Rich, M. M., Lichtman, J. W., J. Neurosci., 9 1989, 1781 ;
21. We thank all the members of our lab for helpful discussion of this work; J. R. Sanes, R. O. Wong, and M. L. Nonet for comments on the manuscript; and S. G. Turney for technical help. This work was supported by grants from NIH and the Muscular Dystrophy Association. W.-B.G. was supported by a National Research Service Award from NIH.

147433738 CA: 147(20)433738c PATENT
Inhibition of calcification on an endovascular device
INVENTOR(AUTHOR): Mckay, William F.
LOCATION: USA
ASSIGNEE: Medtronic Vascular, Inc.
PATENT: U.S. Pat. Appl. Publ. ; US 20070237802 A1 DATE: 20071011
APPLICATION: US 2006279325 (20060411)
PAGES: 8pp. CODEN: USXXCO LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: 424423000
IPCR/8 + Level Value Position Status Version Action Source Office:
A61F-0002/06 A I F B 20060101 20071011 H US
A61K-0038/19 A I L B 20060101 20071011 H US
A61K-0038/18 A I L B 20060101 20071011 H US
SECTION:
CA263007 Pharmaceuticals
IDENTIFIERS: calcification endovascular device
DESCRIPTORS:
Bone morphogenetic proteins...
antagonist, Sclerotin; inhibition of calcification on an endovascular device
Bone morphogenetic proteins... Peptides... Proteins... Transforming growth factor .beta....
antagonist; inhibition of calcification on an endovascular device
Blood vessel...
artificial; inhibition of calcification on an endovascular device
Calcification... Collagens... Cytokines... Elastins... Polysaccharides...
Silk...
inhibition of calcification on an endovascular device
Proteins...
noggin; inhibition of calcification on an endovascular device

Medical goods...
stents; inhibition of calcification on an endovascular device
CAS REGISTRY NUMBERS:
9004-61-9 93566-27-7 inhibition of calcification on an endovascular device

2/7/30 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2008 American Chemical Society. All rts. reserv.

141134077 CA: 141(9)134077u PATENT
Bone morphogenetic protein antagonists for treating vascular inflammation
INVENTOR(AUTHOR): Jo, Hanjoong
LOCATION: USA
ASSIGNEE: Georgia Tech Research Corporation
PATENT: PCT International ; WO 200462621 A2 DATE: 20040729
APPLICATION: WO 2004US759 (20040113) *US PV439667 (20030113)
PAGES: 91 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: A61K-000/A
DESIGNATED COUNTRIES: AE; AE; AG; AL; AL; AM; AM; AM; AT; AT; AU; AU; AZ; AZ; BA; BB; BG; BG; BR; BR; BW; BY; BY; BZ; BZ; CA; CH; CN; CN; CO; CO; CR; CR; CU; CU; CZ; CZ; DE; DE; DK; DK; DM; DZ; EC; EC; EE; EE; EG; ES; ES; FI; FI; GB; GD; GE; GE; GH; GH; GH; GM; HR; HR; HU; HU; ID; IL; IN; IS; JP; JP; KE; KE; KG; KG; KP; KP; KR; KR; KZ; KZ; KZ; LC; LK; LR; LS; LS; LT; LU; LV; MA; MD; MD; MG; MK; MN; MW; MX; MX; MZ
SECTION:
CA201007 Pharmacology
CA203XXX Biochemical Genetics
CA206XXX General Biochemistry
CA213XXX Mammalian Biochemistry
IDENTIFIERS: bone morphogenetic protein BMP antagonist vascular inflammation human
DESCRIPTORS:
Monocyte...
adhesion, inhibition of; bone morphogenetic protein antagonists for treating vascular inflammation
Bone morphogenetic proteins... Bone morphogenetic protein receptors...
antagonist or prodrug; bone morphogenetic protein antagonists for treating vascular inflammation
Antiarteriosclerotics...
antiatherosclerotics; bone morphogenetic protein antagonists for treating vascular inflammation
Anti-inflammatory agents... Gene therapy... Promoter(genetic element)...
Blood vessel... Human... Protein sequences... cDNA sequences... Molecular cloning...
bone morphogenetic protein antagonists for treating vascular inflammation
Protein motifs...
cystine knot; bone morphogenetic protein antagonists for treating vascular inflammation
Blood vessel...
endothelium, promoter-specific for; bone morphogenetic protein antagonists for treating vascular inflammation
Adhesion,biological...
inhibiting, bone morphogenetic protein antagonists for treating vascular inflammation
Proteins...
noggin; bone morphogenetic protein antagonists for treating vascular inflammation
Medical goods...
stents; bone morphogenetic protein antagonists for treating vascular inflammation
Inflammation... Atherosclerosis...
treatment of; bone morphogenetic protein antagonists for treating vascular inflammation
Endothelium...
vascular, promoter-specific for; bone morphogenetic protein antagonists for treating vascular inflammation
Inflammation... Blood vessel,disease...
vasculitis, treatment of; bone morphogenetic protein antagonists for treating vascular inflammation
Proteins...
veinless; bone morphogenetic protein antagonists for treating vascular inflammation
Proteins...
ventroptin; bone morphogenetic protein antagonists for treating vascular inflammation
Bone morphogenetic proteins...
4, antagonist or prodrug; bone morphogenetic protein antagonists for treating vascular inflammation
CAS REGISTRY NUMBERS:
57-88-5 biological studies, lowering agent; bone morphogenetic protein antagonists for treating vascular inflammation
93586-27-7 25191-20-2 bone morphogenetic protein antagonists for treating vascular inflammation
727438-83-7 727438-84-8 727438-85-9 727438-86-0 727438-87-1 cystine knot motif sequence; bone morphogenetic protein antagonists for treating vascular inflammation
727438-78-0P 727438-79-1P 727438-80-4P 727438-81-5P 727438-82-6P nucleotide sequence; bone morphogenetic protein antagonists for treating vascular inflammation
727439-00-1 727439-01-2 727439-02-3 727439-03-4 727439-04-5 727439-05-6 unclaimed nucleotide sequence; bone morphogenetic protein antagonists for treating vascular inflammation
? b 411;set files biotech
22may08 13:09:09 User219511 Session D727.4
$0.39 0.110 DialUnits File155
$0.96 4 Type(s) in Format 7
$0.96 4 Types
$1.35 Estimated cost File155
$0.44 0.071 DialUnits File5
$0.44 Estimated cost File5
$3.77 0.142 DialUnits File34
$15.48 2 Type(s) in Format 7
$15.48 2 Types
$19.25 Estimated cost File34
$1.62 0.126 DialUnits File73
$10.65 3 Type(s) in Format 7
$10.65 3 Types
$12.27 Estimated cost File73
$2.46 0.433 DialUnits File135
$50.70 13 Type(s) in Format 7
$50.70 13 Types
$53.16 Estimated cost File135
$0.64 0.126 DialUnits File144
$5.76 3 Type(s) in Format 7
$5.76 3 Types
$6.40 Estimated cost File144
$0.23 0.063 DialUnits File266
$2.23 1 Type(s) in Format 7
$2.23 1 Types
$2.46 Estimated cost File266
$1.99 0.079 DialUnits File357
$4.31 1 Type(s) in Format 7
$4.31 1 Types
$6.30 Estimated cost File357
$0.26 0.071 DialUnits File370
$1.62 1 Type(s) in Format 7
$1.62 1 Types
$1.88 Estimated cost File370
$1.85 0.142 DialUnits File399
$5.96 2 Type(s) in Format 7
$5.96 2 Types
$7.81 Estimated cost File399
OneSearch, 10 files, 1.362 DialUnits FileOS
$0.26 TELNET
$111.58 Estimated cost this search
$114.46 Estimated total session cost 2.259 DialUnits

```
File 411:DIALINDEX(R)

DIALINDEX(R)
  (c) 2008 Dialog

*** DIALINDEX search results display in an abbreviated ***
*** format unless you enter the SET DETAIL ON command. ***
  You have 25 files in your file list.
  (To see banners, use SHOW FILES command)
? s (bmp-4 or bmp4 or rbmp-4 or rbmp4 or rhbmp-4 or rhbmp4) and ((vascular and inflamm?) or
atherosclero?)

Your SELECT statement is:
  s (bmp-4 or bmp4 or rbmp-4 or rbmp4 or rhbmp-4 or rhbmp4) and ((vascular
and inflamm?) or atherosclero?)

      Items   File
      -----   ----
         20     5: Biosis Previews(R)_1926-2008/May W3
          1     8: Ei Compendex(R)_1884-2008/May W2
          2    24: CSA Life Sciences Abstracts_1966-2008/Mar
         12    34: SciSearch(R) Cited Ref Sci_1990-2008/May W4
          3    45: EMCare_2008/May W3
          8    71: ELSEVIER BIOBASE_1994-2008/May W1
          9    73: EMBASE_1974-2008/May 21
         14   135: NewsRx Weekly Reports_1995-2008/May W3
          6   144: Pascal_1973-2008/May W3
          9   155: MEDLINE(R)_1950-2008/May 21
          2   266: FEDRIP_2008/Feb
          9   357: Derwent Biotech Res._1982-2008/Apr W3
          7   399: CA SEARCH(R)_1967-2008/UD=14821

  13 files have one or more items; file list includes 25 files.

? save temp: b 155,5,71,73,357:exs rd
Temp SearchSave "TC560437308" stored
     22may08 13:10:53 User219511 Session D727.5
       $3.27   1.111 DialUnits File411
    $3.27  Estimated cost File411
    $0.53  TELNET
    $3.80  Estimated cost this search
  $118.26  Estimated total session cost   3.371 DialUnits

SYSTEM:OS - DIALOG OneSearch
  File 155:MEDLINE(R) 1950-2008/May 21
       (c) format only 2008 Dialog
*File 155: MEDLINE has reloaded. Please see HELP NEWS 155
for details.
  File   5:Biosis Previews(R) 1926-2008/May W3
       (c) 2008 The Thomson Corporation
  File  71:ELSEVIER BIOBASE 1994-2008/May W1
       (c) 2008 Elsevier B.V.
  File  73:EMBASE 1974-2008/May 21
       (c) 2008 Elsevier B.V.
*File  73: The 2008 EMTREE Thesaurus has been loaded. Please see
HELP NEWS 72 for details.
  File 357:Derwent Biotech Res. _1982-2008/Apr W3
       (c) 2008 The Thomson Corp.

    Set  Items  Description
    ---  -----  -----------
Executing TC560437308
        297  BMP-4
       3979  BMP4
          1    RBMP-4
          4    RBMP4
          2    RHBMP-4
          6    RHBMP4
    3832631  VASCULAR
    1262528  INFLAMM?
     283716  ATHEROSCLERO?
         S1     55  (BMP-4 OR BMP4 OR RBMP-4 OR RBMP4 OR RHBMP-4 OR RHBMP4)
                  AND ((VASCULAR AND INFLAMM?) OR ATHEROSCLERO?)
         S2     28  RD  (unique items)
? t s2/7/1-28;bye

 2/7/1    (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17854754  PMID: 17785623
   Bone morphogenic protein antagonists are coexpressed with bone
morphogenic protein 4 in endothelial cells exposed to unstable flow in
vitro in mouse aortas and in human coronary arteries: role of bone
morphogenic protein antagonists in %%%inflammation%%% and
%%%atherosclerosis%%%.
   Chang Kyunghwa; Weiss Daiana; Suo Jin; Vega J David; Giddens Don; Taylor
W Robert; Jo Hanjoong
   Wallace H. Coulter Department of Biomedical Engineering, Georgia Tech and
Emory University, Atlanta, GA 30322, USA.
   Circulation (United States) Sep 11 2007, 116 (11) p1258-66, ISSN
1524-4539--Electronic  Journal Code: 0147763
   Contract/Grant No.: HL70531; HL; United States NHLBI; HL75209; HL; United
States NHLBI; U01HL80711; HL; United States NHLBI
   Publishing  Model Print-Electronic;  Comment in Circulation. 2007 Sep
11;116(11) 1221-3; Comment in PMID 17846341
   Document type: Comparative Study; Journal Article; Research Support,
N.I.H., Extramural
   Languages: ENGLISH
   Main Citation Owner: NLM
   Record type: MEDLINE; Completed
   BACKGROUND: Exposure to disturbed flow, including oscillatory shear
stress, stimulates endothelial cells (ECs) to produce bone morphogenic
protein (BMP) 4, which in turn activates %%%inflammation%%%, a critical
atherogenic step. BMP activity is regulated by the level of BMP
antagonists. Until now it was not known whether shear also regulates the
expression of BMP antagonists and whether they play a role in EC
pathophysiology. METHODS AND RESULTS: BMP antagonists follistatin, noggin,
and matrix Gla protein were expressed in cultured bovine and human arterial
ECs. Surprisingly, oscillatory shear stress increased expression of the BMP
antagonists in ECs, whereas unidirectional laminar shear decreased such
expression. Immunohistochemical studies with mouse aortas showed data
consistent with in vitro findings: Only ECs in the lesser curvature exposed
to disturbed flow, but not those in the greater curvature and straight
arterial regions exposed to undisturbed flow, showed coexpression of
%%%BMP4%%% and the BMP antagonists. Similarly, in human coronary arteries,
expression of %%%BMP4%%% and BMP antagonists in ECs positively correlated
with the severity of %%%atherosclerosis%%%. Monocyte adhesion induced by
oscillatory shear stress was inhibited by knockdown of %%%BMP4%%% or
treatment with recombinant follistatin or noggin, whereas it was increased
by knockdown of follistatin and/or noggin. CONCLUSIONS: The present results
suggest that ECs coexpress BMP antagonists along with %%%BMP4%%% in an
attempt to minimize the %%%inflammatory%%% response by oscillatory shear
stress as part of a negative feedback mechanism. The balance between the
agonist, %%%BMP4%%%, and its antagonists may play an important role in the
overall control of %%%inflammation%%% and %%%atherosclerosis%%%.
   Record Date Created: 20070911
   Record Date Completed: 20071011
   Date of Electronic Publication: 20070904

 2/7/2    (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17375299  PMID: 17030628
   Bone morphogenetic protein-induced MSX1 and MSX2 inhibit
myocardin-dependent smooth muscle gene transcription.
   Hayashi Ken'ichiro; Nakamura Seiji; Nishida Wataru; Sobue Kenji
   Department of Neuroscience (D13), Osaka University Graduate School of
```

Medicine, Yamadaoka 2-2, Suita, Osaka 565-0871, Japan.
Molecular and cellular biology (United States) Dec 2006, 26 (24) p9456-70, ISSN 0270-7306--Print Journal Code: 8109087
Publishing Model Print-Electronic
Document type: Journal Article, Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
During the onset and progression of %%%atherosclerosis%%%, the vascular smooth muscle cell (VSMC) phenotype changes from differentiated to dedifferentiated, and in some cases, this change is accompanied by osteogenic transition, resulting in vascular calcification. One characteristic of dedifferentiated VSMCs is the down-regulation of smooth muscle cell (SMC) marker gene expression. Bone morphogenetic proteins (BMPs), which are involved in the induction of osteogenic gene expression, are detected in calcified vasculature. In this study, we found that the BMP2-, %%%BMP4%%%-, and BMP6-induced expression of Msx transcription factors (Msx1 and Msx2) preceded the down-regulation of SMC marker expression in cultured differentiated VSMCs. Either Msx1 or Msx2 markedly reduced the myocardin-dependent promoter activities of SMC marker genes (SM22alpha and caldesmon). We further investigated interactions between Msx1 and myocardin/serum response factor (SRF)/CArG-box motif (cis element for SRF) using coimmunoprecipitation, gel-shift, and chromatin immunoprecipitation assays. Our results showed that Msx1 or Msx2 formed a ternary complex with SRF and myocardin and inhibited the binding of SRF or SRF/myocardin to the CArG-box motif, resulting in inhibition of their transcription.
Record Date Created: 20061130
Record Date Completed: 20070124
Date of Electronic Publication: 20061009

2/7/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17255697 PMID: 16987015
Role of NADPH oxidases in disturbed flow- and %%%BMP4%%%- induced inflammation and %%%atherosclerosis%%%.
Jo Hanjoong; Song Hannah; Mowbray Amy
Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, 30322, USA. hanjoong.jo@bme.gatech.edu
Antioxidants & redox signaling (United States) Sep-Oct 2006, 8 (9-10) p1609-19, ISSN 1523-0864--Print Journal Code: 100888899
Contract/Grant No.: HL67413: HL; United States NHLBI; HL71014: HL; United States NHLBI; P01HL075209: HL; United States NHLBI
Publishing Model Print
Document type: Journal Article, Research Support, N.I.H., Extramural; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
%%%Atherosclerosis%%% is an inflammatory disease, occurring preferentially in branched or curved arterial regions exposed to disturbed flow conditions including oscillatory shear stress (OS). In contrast, straight portions exposed to undisturbed laminar shear stress (LS) are relatively lesion free. The opposite effects of atheroprotective LS and proatherogenic OS are likely to be determined by differential expression of genes and proteins, including redox regulating factors. OS induces inflammation via mechanisms involving increased reactive oxygen species (ROS) production from the NADPH oxidases. Through a transcript profiling study and subsequent verification and functional studies, the authors discovered that OS induces inflammation by producing bone morphogenic protein 4 (%%%BMP4%%%) in endothelial cells. %%%BMP4%%% stimulates expression and activity of NADPH oxidase requiring p47phox and Nox-1 in an autocrine-like manner. The NADPH oxidase activation by %%%BMP4%%% then leads to ROS production, NF-kappaB activation, intercellular adhesion molecule 1 (ICAM-1) expression, and subsequent increased monocyte adhesivity of endothelial cells. It is proposed that endothelial NADPH oxidases play a critical role in disturbed flow- and %%%BMP4%%%-dependent inflammation, which is the critical early atherogenic response occurring in atheroprone areas. This emerging field of shear stress, %%%BMP4%%%, NADPH oxidases, inflammation, and %%%atherosclerosis%%% is reviewed. (102 Refs.)
Record Date Created: 20060921
Record Date Completed: 20070104

2/7/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17099643 PMID: 16601233
Molecular mechanisms of %%%vascular%%% calcification: lessons learned from the aorta.
Shao Jian-Su; Cai Jun; Towler Dwight A
Washington University School of Medicine, Campus Box 8301, 660 South Euclid Ave, St. Louis, MO 63110, USA.
Arteriosclerosis, thrombosis, and vascular biology (United States) Jul 2006, 26 (7) p1423-30, ISSN 1524-4636--Electronic Journal Code: 9505803
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
%%%Vascular%%% calcification increasingly afflicts our aging and dysmetabolic population. Once considered a passive process, it has emerged as an actively regulated form of calcified tissue metabolism, resembling the mineralization of endochondral and membranous bone. Executive cell types familiar to bone biologists, osteoblasts, chondrocytes, and osteoclasts, are seen in calcifying macrovascular specimens. Lipidaceous matrix vesicles, with biochemical and ultrastructural "signatures" of skeletal matrix vesicles, nucleate %%%vascular%%% mineralization in diabetes, dyslipidemia, and uremia. Skeletal morphogens (bone morphogenetic protein-2 (BMP) and %%%BMP4%%% and Wnts) divert aortic mesangioblasts, mural pericytes (calcifying %%%vascular%%% cells), or valve myofibroblasts to osteogenic fates. Paracrine signals provided by these molecules mimic the epithelial-mesenchymal interactions that induce skeletal development. %%%Vascular%%% expression of pro-osteogenic morphogens is entrained to physiological stimuli that promote calcification. %%%Inflammation%%%, shear, oxidative stress, hyperphosphatemia, and elastinolysis provide stimuli that: (1) promote %%%vascular%%% BMP2/4 signaling and matrix remodeling; and (2) compromise %%%vascular%%% defenses that limit calcium deposition, inhibit osteo/chondrogenic trans-differentiation, and enhance matrix vesicle clearance. In this review, we discuss the biology of %%%vascular%%% calcification. We highlight how aortic fibrofatty tissue expansion (adventitia, valve interstitium), the adventitial-medial vasa, %%%vascular%%% matrix, and matrix vesicle metabolism contribute to the regulation of aortic calcium deposition, with greatest emphasis placed on diabetic %%%vascular%%% disease. (85 Refs.)
Record Date Created: 20060623
Record Date Completed: 20060718
Date of Electronic Publication: 20060406

2/7/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17093421 PMID: 16769910
Bone morphogenic protein-4 induces hypertension in mice: role of noggin, %%%vascular%%% NADPH oxidases, and impaired vasorelaxation.
Miriyala Sumitra; Gongora Nieto Maria C; Mingone Christopher; Smith Debra ; Dikalov Sergey; Harrison David G; Jo Hanjoong
Division of Cardiology, Emory University, Emory University, Atlanta, GA 30322, USA.
Circulation (United States) Jun 20 2006, 113 (24) p2818-25, ISSN 1524-4539--Electronic Journal Code: 0147763

Contract/Grant No.: HL075209, HL; United States NHLBI, HL30096, HL; United States NHLBI, HL58000, HL; United States NHLBI, HL71014, HL; United States NHLBI

Publishing Model Print-Electronic

Document type: Journal Article, Research Support, N.I.H., Extramural

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE, Completed

BACKGROUND. Recent in vitro studies have shown that disturbed flow and oxidative conditions induce the expression of bone morphogenic proteins (BMPs 2 and 4) in cultured endothelial cells. BMPs can stimulate superoxide production and %%%inflammatory%%% responses in endothelial cells, raising the possibility that BMPs may play a role in %%%vascular%%% diseases such as hypertension and %%%atherosclerosis%%%. In this study, we examined the hypothesis that %%%BMP4%%% would induce hypertension in intact animals by increasing superoxide production from %%%vascular%%% nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and an impairment of vasodilation responses. METHODS AND RESULTS: %%%BMP4%%% infusion by osmotic pumps increased systolic blood pressure in a time- and dose-dependent manner in both C57BL/6 mice (from 101 to 125 mm Hg) and apolipoprotein E-null mice (from 107 to 146 mm Hg) after 4 weeks. Cotreatment with the BMP antagonist noggin or the NADPH oxidase inhibitor apocynin completely blocked the %%%BMP4%%% effect. In addition, %%%BMP4%%% infusion stimulated aortic NADPH oxidase activity and impaired vasorelaxation, both of which were prevented either by coinfusing noggin or by treating the isolated aortas with apocynin. %%%BMP4%%%, however, did not cause significant changes in maximum relaxation induced by the endothelium-independent vasodilator nitroglycerin. Remarkably, %%%BMP4%%% infusion failed to stimulate aortic NADPH oxidases, increase blood pressure, and impair vasodilation responses in p47phox-deficient mice. CONCLUSIONS: These results suggest that %%%BMP4%%% infusion induces hypertension in mice in a %%%vascular%%% NADPH oxidase-dependent manner and the subsequent endothelial dysfunction. We suggest that %%%BMP4%%% is a novel mediator of endothelial dysfunction and hypertension and that noggin and its analogs could be used as therapeutic agents for treating %%%vascular%%% diseases.

Record Date Created: 20060620

Record Date Completed: 20060717

Date of Electronic Publication: 20060612

2/7/6 (Item 6 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 2008 Dialog. All rts. reserv.

17051255 PMID: 16601225

Thrombin and NAD(P)H oxidase-mediated regulation of CD44 and %%%BMP4%%% -Id pathway in VSMC, restenosis, and %%%atherosclerosis%%%.

Vendrov Aleksandr E; Madamanchi Nageswara R; Hakim Zeenat S; Rojas Mauricio; Runge Marschall S

Carolina Cardiovascular Biology Center, Department of Medicine, University of North Carolina, Chapel Hill, NC 27599-7055, USA.

Circulation research (United States) May 26 2006, 98 (10) p1254-63, ISSN 1524-4571--Electronic Journal Code: 0047103

Contract/Grant No.: HL57352, HL; United States NHLBI

Publishing Model Print-Electronic

Document type: Journal Article; Research Support, N.I.H., Extramural

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE, Completed

To characterize novel signaling pathways that underlie NAD(P)H oxidase-mediated signaling in %%%atherosclerosis%%%, we first examined differences in thrombin-induced gene expression between wild-type and p47phox(-/-) (NAD[P]H oxidase-deficient) VSMC. Of the 9000 genes analyzed by cDNA microarray method at the G1/S transition point, 76 genes were similarly and significantly modulated in both the cell types, whereas another 22 genes that encompass various functional groups were regulated in NAD(P)H oxidase-dependent manner. Among these 22 genes, thrombin-induced NAD(P)H oxidase-mediated regulation of Klf15, Igbp1, Ak4, Adamts5, Ech1, Serp1, Sec61a2, Aox1, Aoh1, Fxyd5, Rai14, and Serpinh1 was shown for the first time in VSMC. The role of NAD(P)H oxidase in the regulation of a subset of these genes (CD44, %%%BMP4%%%, Id1, and Id3) was confirmed using modulators of reactive oxygen species (ROS) generation, a ROS scavenger and in gain-of-function experiments. We then characterized regulation of these genes in restenosis and %%%atherosclerosis%%%. In both apoE(-/-) mice and in a mouse vascular injury model, these genes are regulated in NAD(P)H oxidase-dependent manner during vascular lesion formation. Based on these findings, we propose that NAD(P)H oxidase-dependent gene expression in general, and the CD44 and %%%BMP4%%%-Id signaling pathway in particular, is important in restenosis and %%%atherosclerosis%%%.

Record Date Created: 20060526

Record Date Completed: 20060612

Date of Electronic Publication: 20060406

2/7/7 (Item 7 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 2008 Dialog. All rts. reserv.

16014745 PMID: 15388638

Bone morphogenic protein 4 produced in endothelial cells by oscillatory shear stress induces monocyte adhesion by stimulating reactive oxygen species production from a nox1-based NADPH oxidase.

Sorescu George P; Song Hannah; Tressel Sarah L; Hwang Jinah; Dikalov Sergey; Smith Debra A; Boyd Nolan L; Platt Manu O; Lassegue Bernard; Griendling Kathy K; Jo Hanjoong

Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, Ga 30322, USA.

Circulation research (United States) Oct 15 2004, 95 (8) p773-9, ISSN 1524-4571--Electronic Journal Code: 0047103

Contract/Grant No.: HL67413, HL; United States NHLBI; HL71014, HL; United States NHLBI; P01HL075209, HL; United States NHLBI

Publishing Model Print-Electronic

Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE, Completed

%%%Atherosclerosis%%% is an %%%inflammatory%%% disease occurring preferentially in arterial regions exposed to disturbed flow conditions including oscillatory shear stress (OS). OS exposure induces endothelial expression of bone morphogenic protein 4 (%%%BMP4%%%), which in turn may activate intercellular adhesion molecule-1 (ICAM-1) expression and monocyte adhesion. OS is also known to induce monocyte adhesion by producing reactive oxygen species (ROS) from reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, raising the possibility that %%%BMP4%%% may stimulate the %%%inflammatory%%% response by ROS-dependent mechanisms. Here we show that ROS scavengers blocked ICAM-1 expression and monocyte adhesion induced by %%%BMP4%%% or OS in endothelial cells (ECs). Similar to OS, %%%BMP4%%% stimulated H2O2 and O2- production in ECs. Next, we used ECs obtained from p47phox-/- mice (MAE-p47-/-), which do not produce ROS in response to OS, to determine the role of NADPH oxidases. Similar to OS, %%%BMP4%%% failed to induce monocyte adhesion in MAE-p47-/-, but it was restored when the cells were transfected with p47phox plasmid. Moreover, OS-induced O2- production was blocked by noggin (a BMP antagonist), suggesting a role for BMP. Furthermore, OS increased gp91phox (nox2) and nox1 mRNA levels while decreasing nox4. In contrast, %%%BMP4%%% induced nox1 mRNA expression, whereas nox2 and nox4 were decreased or not affected, respectively. Also, OS-induced monocyte adhesion was blocked by knocking down nox1 with the small interfering RNA (siRNA). Finally, %%%BMP4%%% siRNA inhibited OS-induced ROS production and monocyte adhesion. Together, these results suggest that %%%BMP4%%% produced in ECs by OS stimulates ROS release from the nox1-dependent NADPH oxidase leading to %%%inflammation%%%, a critical early atherogenic step.

Record Date Created: 20041015

Record Date Completed: 20050428

Date of Electronic Publication: 20040923

2/7/8 (Item 8 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 2008 Dialog. All rts. reserv.

15316665 PMID: 12766166
Bone morphogenic protein 4 produced in endothelial cells by oscillatory shear stress stimulates an %%%inflammatory%%% response
Sorescu George P, Sykes Michelle, Weiss Daiana, Platt Manu O, Saha Aniket , Hwang Jinah, Boyd Nolan, Boo Yong C, Vega J David, Taylor W Robert, Jo Hanjoong Jo H GA Inst Technol, Atlanta
Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University, Atlanta, Georgia 30322, USA.
Journal of biological chemistry (United States) Aug 15 2003, 278 (33) p31128-35, ISSN 0021-9258--Print Journal Code: 2985121R
Contract/Grant No.: HL67413; HL; United States NHLBI; HL70531; HL; United States NHLBI; HL71014; HL; United States NHLBI
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, Non-P.H.S.; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
%%%Atherosclerosis%%% is now viewed as an %%%inflammatory%%% disease occurring preferentially in arterial regions exposed to disturbed flow conditions, including oscillatory shear stress (OS), in branched arteries. In contrast, the arterial regions exposed to laminar shear (LS) are relatively lesion-free. The mechanisms underlying the opposite effects of OS and LS on the %%%inflammatory%%% and atherogenic processes are not clearly understood. Here, through DNA microarrays, protein expression, and functional studies, we identify bone morphogenic protein 4 (%%%BMP4%%%) as a mechanosensitive and pro-%%%inflammatory%%% gene product. Exposing endothelial cells to OS increased %%%BMP4%%% protein expression, whereas LS decreased it. In addition, we found %%%BMP4%%% expression only in the selective patches of endothelial cells overlying foam cell lesions in human coronary arteries. The same endothelial patches also expressed higher levels of intercellular cell adhesion molecule-1 (ICAM-1) protein compared with those of non-diseased areas. Functionally, we show that OS and %%%BMP4%%% induced ICAM-1 expression and monocyte adhesion by a NFkappaB-dependent mechanism. We suggest that %%%BMP4%%% is a mechanosensitive, %%%inflammatory%%% factor playing a critical role in early steps of atherogenesis in the lesion-prone areas.
Record Date Created: 20030811
Record Date Completed: 20031110
Date of Electronic Publication: 20030523

2/7/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

14231026 PMID: 11521229
Mast cell involvement in fibrodysplasia ossificans progressiva.
Gannon F H; Glaser D; Caron R; Thompson L D; Shore E M; Kaplan F S
Department of Orthopaedic Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA.
Human pathology (United States) Aug 2001, 32 (8) p842-8, ISSN 0046-8177--Print Journal Code: 9421547
Contract/Grant No.: 2-RO1-AR-41916; AR; United States NIAMS
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
Fibrodysplasia ossificans progressiva (FOP) is a catastrophic genetic disorder of progressive heterotopic ossification associated with dysregulated production of bone morphogenetic protein 4 (%%%BMP4%%%), a potent osteogenic morphogen. Postnatal heterotopic ossification in FOP is often heralded by hectic episodes of severe post-traumatic connective tissue swelling and intramuscular edema, followed by an intense and highly angiogenic fibroproliferative mass. The abrupt appearance, intense size, and rapid intrafascial spread of the edematous preosseous fibroproliferative lesions implicate a dysregulated wound response mechanism and suggest that cells and mediators involved in %%%inflammation%%% and tissue repair may be conscripted in the growth and progression of FOP lesions. The central and coordinate role of %%%inflammatory%%% mast cells and their mediators in tissue edema, wound repair, fibrogenesis, angiogenesis, and tumor invasion prompted us to investigate the potential involvement of mast cells in the pathology of FOP lesions. We show that %%%inflammatory%%% mast cells are present at every stage of the development of FOP lesions and are most pronounced at the highly %%%vascular%%% fibroproliferative stage. Mast cell density at the periphery of FOP lesional tissue is 40- to 150-fold greater than in normal control skeletal muscle or in uninvolved skeletal muscle from FOP patients and 10- to 40-fold greater than in any other %%%inflammatory%%% myopathy examined. These findings document mobilization and activation of %%%inflammatory%%% mast cells in the pathology of FOP lesions and provide a novel and previously unrecognized target for pharmacologic intervention in this extremely disabling disease.
Record Date Created: 20010824
Record Date Completed: 20010927

2/7/10 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

0019897047 BIOSIS NO.: 200700556788
Valvular endothelial cells and the mechanoregulation of valvular pathology
AUTHOR: Butcher Jonathan T (Reprint); Nerem Robert M
AUTHOR ADDRESS: Cornell Univ, Dept Biomed Engn, 270 Olin Hall, Ithaca, NY 14850 USA**USA
AUTHOR E-MAIL ADDRESS: jtb47@cornell.edu
JOURNAL: Philosophical Transactions of the Royal Society of London B Biological Sciences 362 (1484): p1445-1457 AUG 29 2007 2007
ITEM IDENTIFIER: doi:10.1098/rstb.2007.2127
ISSN: 0962-8436
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Endothelial cells are critical mediators of haemodynamic forces and as such are important foci for initiation of vascular pathology. Valvular leaflets are also lined with endothelial cells, though a similar role in mechanosensing has not been demonstrated. Recent evidence has shown that valvular endothelial cells respond morphologically to shear stress, and several studies have implicated valvular endothelial dysfunction in the pathogenesis of disease. This review seeks to combine what is known about vascular and valvular haemodynamics, endothelial response to mechanical stimuli and the pathogenesis of valvular diseases to form a hypothesis as to how mechanical stimuli can initiate valvular endothelial dysfunction and disease progression. From this analysis, it appears that inflow surface-related bacterial/thrombotic vegetative endocarditis is a high shear-driven endothelial denudation phenomenon, while the outflow surface with its related calcific%%%atherosclerotic%%% degeneration is a low/oscillatory shear-driven endothelial activation phenomenon. Further understanding of these mechanisms may help lead to earlier diagnostic tools and therapeutic strategies.

2/7/11 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

0019483282 BIOSIS NO.: 200700143023
Effect of p47phox-based NADPH oxidases on shear stress-dependent gene expression profiles in endothelial cells
AUTHOR: Sykes Michelle (Reprint); Jo Hanjoong
AUTHOR ADDRESS: Georgia Inst Technol, Atlanta, GA 30332 USA**USA
JOURNAL: Free Radical Biology & Medicine 41 (Suppl. 1): pS43 2006 2006
CONFERENCE/MEETING: 13th Annual Meeting of the

Society-for-Free-Radical-Biology-and-Medicine Denver, CO, USA November 15 -19, 2006, 20061115
SPONSOR: Soc Free Rad Biol & Med
ISSN: 0891-5849
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/12 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

0019462404 BIOSIS NO.: 200700122145
The BMP receptor II is localized in the endothelial cell junction and plays a paradoxical role as both a pro- and an anti-%%%inflammatory%%% regulator
AUTHOR: Song Hannah (Reprint); Jo Hanjoong
AUTHOR ADDRESS: Georgia Inst Technol, Atlanta, GA 30332 USA**USA
JOURNAL: Circulation 114 (18, Suppl. S): p320 OCT 31 2006 2006
CONFERENCE/MEETING: 79th Annual Scientific Session of the American-Heart-Association Chicago, IL, USA November 12 -15, 2006; 20061112
SPONSOR: Amer Heart Assoc
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Atherosclerosis%%% is known as an %%%inflammatory%%% disease, occurring preferentially in branched or curved arteries associated with unstable flow including oscillatory shear stress (OS). We have shown that bone morphogenic protein 4 (%%%BMP4%%%) produced in endothelial cells by OS stimulates %%%inflammatory%%% responses as determined by ICAM-1 induction and monocyte adhesion. To determine the mechanism by which %%%BMP4%%% induces the %%%inflammatory%%% response, we examined which BMP receptors are expressed in mouse aortic endothelial cells (MAEC) and mouse aortas. RT-PCR, Western blot, and immunohistochemical staining analyses revealed that BMPRI (ALK2) and BMPRII are the major BMP receptors expressed in MAEC and mouse thoracic aortic endothelium. Interestingly, BMPRII is found mainly in the endothelial cell-cell junction, colocalizing with VE-cadherin, in confluent MAEC but not in subconfluent or wounded cells. Knocking down BMPRII protein levels by siRNA prevented %%%BMP4%%%-induced monocyte adhesion to MAEC and human umbilical vein EC (HUVEC), suggesting the essential role of BMPRII in %%%BMP4%%%-induced %%%inflammation%%%. Unexpectedly, however, the BMPRII-knockdown also significantly increased monocyte adhesion and ICAM-1 expression in the basal condition in comparison to the non-silencing control. Monocyte adhesion induced by BMPRII knockdown was abolished by the YN1 ICAM-1 blocking antibody. These results suggest that the BMPRII plays a paradoxical role: one that mediates %%%inflammation%%% upon %%%BMP4%%% binding and another that constitutively prevents %%%inflammation%%% in the basal condition as revealed by the siRNA study. Since the loss-of-function mutations of BMPRII are known to induce primary pulmonary hypertension, a disease characterized by uncontrolled endothelial proliferation and %%%inflammation%%%, it is important to study whether our findings are involved in this disease as well as %%%atherosclerosis%%%.

2/7/13 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

18992107 BIOSIS NO.: 200600337502
Induction of %%%BMP4%%% in %%%vascular%%% smooth muscle cells by shear stress
AUTHOR: Rouhanizadeh Mahsa (Reprint); Lin Tiantian C; Miller Jordan D; Heistad Donald; Hsiai Tzung K
AUTHOR ADDRESS: Univ Iowa, Div Cardiovasc, Iowa City, IA 52242 USA**USA
JOURNAL: FASEB Journal 20 (5, Part 2): pA1176-A1177 MAR 7 2006 2006
CONFERENCE/MEETING: Experimental Biology 2006 Meeting San Francisco, CA, USA April 01 -05, 2006; 20060401
SPONSOR: Amer Assoc Anatomists
Amer Physiol Soc
Amer Soc Biochem & Mol Biol
Amer Soc Investigat Pathol
Amer Soc Nutr
Amer Soc Pharmacol & Expt Therapeut
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Bone morphogenic protein-4 (%%%BMP4%%%) promotes %%%inflammatory%%% responses and %%%vascular%%% calcification. Smooth muscle cells proliferation and migration occur in the denuded arteries post angioplasty. We assessed whether pulsatile shear stress (PSS) vs. oscillatory shear stress (OSS) regulated BMP2 and %%%BMP4%%% expression in bovine aortic endothelial cell (BAEC) and %%%vascular%%% smooth muscle cell (VSMC).Methods: Confluent BAEC and VSMC monolayers were exposed to PSS at a mean shear stress (tau(ave)) of 23 dyn.cm(-2) and a temporal gradient (delta tau/delta tau) at 71 dyn.cm(-2).sec(-2); and OSS at tau(ave) = 0.02 3 dyn.cm(-2) in a dynamic parallel plate flow system for 4 hours. BMP-mRNA was measured with real-time RT-PCR.Results: a) VSMC (Fig. 1): OSS significantly up-regulated %%%BMP4%%% by 2.2-fold and PSS by 1.64-fold (P<0.05, n=3) in VSMC. OSS significantly downregulated BMP2 by 0.32-fold (P < 0.05), but PSS-induced downregulation was statistically insignificant. Control samples were under static condition.[GRAPHICS]Fig. 1. Smooth Muscle cell BMP mRNA expression b) BAEC (Fig. 2): OSS up-regulated BMP2 by 2-fold, and %%%BMP4%%% by 1.5-fold in BAEC. Similarly, PSS induced BMP2 and %%%BMP4%%% expression by 1.6- and 1.4-fold, respectively. However, these differences were statistically insignificant.[GRAPHICS]Fig. 2. Endothelial BMP mRNA expression Discussion: OSS was a stronger inducer of %%%BMP4%%% expression in VSMC than PSS. The findings suggest that shear stress mediated increases in %%%BMP4%%% expression may contribute to %%%inflammation%%% in the denuded regions of stented arteries.

2/7/14 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

18701996 BIOSIS NO.: 200600047391
Thrombin-induced reactive oxygen species-dependent gene expression in %%%atherosclerosis%%% and vascular injury
AUTHOR: Vendrov Aleksandr E (Reprint); Hakim Zeenat S; Madamanchi Nageswara R; Runge Marschall S
AUTHOR ADDRESS: Univ N Carolina, Chapel Hill, NC USA**USA
JOURNAL: Circulation 112 (17, Suppl. S): pU346 OCT 25 2005 2005
CONFERENCE/MEETING: 78th Annual Scientific Session of the American-Heart-Association Dallas, TX, USA November 13 -16, 2005; 20051113
SPONSOR: Amer Heart Assoc
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/15 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

18620437 BIOSIS NO.: 200510314937
ROS-dependent gene regulation in vascular smooth muscle cells (VSMC): Signals that modulate VSMC and vascular function
AUTHOR: Vendrov Aleksandr E (Reprint); Hakim Zeenat S; Mehrizi Ali; Tchivilev Igor; Madamanchi Nageswara R; Runge Marschall S

AUTHOR ADDRESS: Univ N Carolina, Chapel Hill, NC USA**USA
JOURNAL: Circulation 110 (17, Suppl. S): p283-284 OCT 26 2004 2004
CONFERENCE/MEETING: 77th Scientific Meeting of the American-Heart-Association New Orleans, LA, USA November 07 -10, 2004; 20041107
SPONSOR: Amer Heart Assoc
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Vascular smooth muscle cells (VSMC) are dependent upon reactive oxygen species (ROS) for growth. Thrombin-treated VSMC from p47phox-/- (NAD(P)H oxidase-deficient) mice have attenuated ROS generation and proliferation compared to wild-type VSMC. Moreover, apoE-/-/p47phox-/- mice had less %%%atherosclerosis%%% than apoE-/- mice. For a comprehensive understanding of the transcriptional events that mediate ROS-dependent mitogenesis, we used cDNA microarray analysis to characterize gene expression profiles of VSMC treated with thrombin. Analysis was performed on wild-type, p47phox-/- and gp91phox-/- VSMC (possess Nox1/4 functional homolog, hence oxidase activity). Analysis of 9,000 genes on microarray by Significance Analysis of Microarray (SAM) revealed a subset of 28 genes in wild-type and gp91phox-/- VSMC with significant changes in expression (Delta 0.03) as compared to p47phox-/VSMC. Real-time PCR analysis confirmed 22 out of 28 genes identified by SAM. These redox-sensitive genes encode proteins with diverse functions; cell proliferation and apoptosis (BMP and Wnt signaling pathway, Rit1), extracellular matrix modulation (tissue inhibitor of metalloproteinase 3), and cell adhesion and signal transduction (CD44 antigen). The redox-sensitive regulation of these genes was corroborated in wild-type and p47phox-/- VSMC treated with 2,3-dimethoxy-1,4-naphtoquinone. The role of NAD(P)H oxidase function was confirmed by gain of function experiments in which transduction of p47phox-/- VSMC with adenoviral vector containing human p47phox cDNA restored thrombin-induced regulation of the subset of the redox-sensitive genes to near wild-type levels. The expression profile of several genes is similar in all three cell types suggesting that thrombin also caused NAD(P)H oxidase-independent gene regulation. %%%BMP4%%% and its transcriptional targets Id1 and Id3 were significantly down-regulated in wild-type but not in p47phox-/- VSMC treated with thrombin and %%%BMP4%%% treatment up-regulated Id1and Id3 in both cell types which corroborates that ROS modulate growth. In conclusion, cDNA microarray analysis identified new NAD(P)H oxidase-dependent and -independent thrombin-responsive genes that may be important in vascular lesion formation.

2/7/16 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

18290622 BIOSIS NO.: 200500197687
Expression of bone morphogenic protein 2/4, transforming growth factor-beta1, and bone matrix protein expression in healing area between %%%vascular%%% tibia grafts and irradiated bone - Experimental model of osteonecrosis
AUTHOR: Schultze-Mosgau Stefan (Reprint); Lehner Bernhard; Roedel Franz; Wehrhan Falk; Amann Kerstin; Kopp Juergen; Thorwarth Michael; Nkenke Emeka; Grabenbauer Gerhard
AUTHOR ADDRESS: Dept Oral and Maxillofacial Surg, Univ Erlangen Nurnberg, Gluecksstr 11, D-91054, Erlangen, Germany**Germany
AUTHOR E-MAIL ADDRESS: stefan.schultz-mosgau@mkg.imed.uni-erlangen.de
JOURNAL: International Journal of Radiation Oncology Biology Physics 61 (4): p1189-1196 March 15, 2005 2005
MEDIUM: print
ISSN: 0360-3016 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose: For the surgical treatment of osteoradionecrosis after multimodal therapy of head-and-neck cancers, free %%%vascular%%% bone grafts are used to reconstruct osseous structures in the previously irradiated graft bed. Reduced, or even absent osseous healing in the transition area between the %%%vascular%%% graft and the irradiated graft bed represents a clinical problem. %%%Inflammatory%%% changes and fibrosis lead to delayed healing, triggered by bone morphogentic protein 2/4 (BMP2/4) and transforming growth factor (TGF)-beta1. Given the well-known fibrosis-inducing activity of TGF-beta1, an osteoinductive effect has been reported for BMP2/4. However, the influence of irradiation (RT) on this cytokine expression remains elusive. Therefore, the aim of the present in vivo study was to analyze the expression of BMP2/4, TGF-beta1, collagen I, and osteocalcin in the transition area between the bone graft and the graft bed after RT. Methods and Materials: Twenty Wistar rats (male, weight 300-500 g) were used in this study. A free %%%vascular%%% tibia graft was removed in all rats and maintained pedicled in the groin region. Ten rats underwent RT with 5 X 10 Gy to the right tibia, the remainder served as controls. After 4 weeks, the previously removed tibia grafts were regrafted into the irradiated (Group 1) and nonirradiated (Group 2) graft beds. The interval between RT and grafting was 4 weeks. After a 4-week osseous healing period, the bone grafts were removed, and the transition area between the nonirradiated graft and the irradiated osseous graft bed was examined histomorphometrically (National Institutes of Health imaging program) and immunohistochemically (avidin-biotin-peroxidase complex) for the expression of BMP2/4, TGF-beta1, collagen 1, and osteocalcin. Results: Absent or incomplete osseous healing of the graft was found in 9 of 10 rats after RT with 50 Gy and in 1 of 10 of the rats with nonirradiated osseous grafts. Histomorphometrically, the proportion of osseous healing in the transition area was 17% in Group 1 and 48% in Group 2 (P = 0.001). Compared with the nonirradiated rats, reduced enchondral and perichondral ossification was found in the healing area after RT, with a reduction of BMP2/4 and osteocalcin expression. TGF-beta1 and collagen I expression in the transition area to the irradiated osseous graft bed was significantly increased compared with that in the nonirradiated osseous graft bed. Conclusion: After RT, osseous healing of %%%vascular%%% bone grafts is significantly reduced and may be a result of radiation-induced inhibition of BMP2/4 and osteocalcin expression. In addition, induction of TGF-beta1 and collagen I expression occurs. Because the effects of the TGF-beta superfamily are manifold and partially unknown, additional research directions could be in the exogenous application of BMP2/4 and inhibition of TGF-beta1 by antibody treatment to search for appropriate therapeutic approaches for improving osseous healing in the irradiated graft bed. Copyright 2005 Elsevier Inc.

2/7/17 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

17922077 BIOSIS NO.: 200400291034
Bone morphogenic protein 4 (%%%BMP4%%%) produced in endothelial cells (EC) by oscillatory shear (OS) induces monocyte adhesion by a redox sensitive manner
AUTHOR: Sorescu George P (Reprint); Hwang Jinah; Dikalov Sergey I; Smith Debra A; Tressel Sarah L; Jo Hanjoong
AUTHOR ADDRESS: BME, GA Tech/Emory University, 1639 Pierce Drive, WMB Rm 3310, Atlanta, GA, 30322, USA**USA
AUTHOR E-MAIL ADDRESS: gsoresc@emory.edu
JOURNAL: FASEB Journal 18 (4-5): pAbst. 277.4 2004 2004
MEDIUM: e-file
CONFERENCE/MEETING: FASEB Meeting on Experimental Biology: Translating the Genome Washington, District of Columbia, USA April 17-21, 2004; 20040417
SPONSOR: FASEB
ISSN: 0892-6638 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Atherosclerosis%%% is an %%%inflammatory%%% disease occurring

preferentially in arterial regions exposed to disturbed flow conditions including OS. Recently, we have shown that OS triggers %%%BMP4%%% expression in EC (Soresc u et al. J Biol Chem 278-31128, 2003). OS-induced %%%BMP4%%% was then responsible for monocyte adhesion (a critical early step in atherogenesis) by inducing intercellular adhesion molecule-1 (ICAM-1) expression. Here, we tested the hypothesis that %%%BMP4%%% stimulates the %%%inflammatory%%% response by reactive oxygen species (ROS)-dependent mechanisms. Treatment of EC with ROS scavengers (PEG-Catalase, Tiron, and N-Acetyl Cysteine) blocked ICAM-1 expression and monocyte adhesion induced by either %%%BMP4%%% or OS. Both OS and %%%BMP4%%% stimulated H2O2 (DCF-DA assay) and O2- (ESR assay using CMH) production in EC. Moreover, OS-induced O2- production was blocked by pre-treating EC with noggin (a %%%BMP4%%% antagonist), suggesting a role for %%%BMP4%%%. To further confirm the identity and source of ROS, EC were obtained from p47phox NADH oxidase knockout mice (MAE-p47-/-). %%%BMP4%%% failed to induce ICAM-1 expression and monocyte adhesion in MAE-p47-/-. Both %%%inflammatory%%% responses were restored by transfecting them with p47phox plasmid. These results demonstrate that %%%BMP4%%% is a mechanosensitive, pro-%%%inflammatory%%% cytokine inducing monocyte adhesion by stimulating ROS production from NADPH oxidase in EC. .

2/7/18 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

17693220 BIOSIS NO.: 200400063977
Bybone morphogenic protein 4 (%%%BMP4%%%) produced in endothelial cells (EC) by oscillatory shear (OS) induces monocyte adhesion by a redox sensitive manner.
AUTHOR: Soresc u George; Hwang Jinah; Dikalov Sergey; Jo Hanjoong
JOURNAL: Free Radical Biology & Medicine 35 (Supplement 1): pS57 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 10th Annual Meeting of the Society for Free Radical Biology and Medicine Seattle, WA, USA November 20-24, 2003; 20031120
ISSN: 0891-5849 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/19 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

17399958 BIOSIS NO.: 200300358677
Bone morphogenic protein-4 (%%%BMP4%%%) induced by oscillatory shear mediates monocyte adhesion to endothelial cells - a novel role of %%%BMP4%%% in %%%inflammatory%%% response and %%%atherosclerosis%%%.
AUTHOR: Soresc u G P (Reprint); Sykes M; Weiss D; Platt M O; Boyd N L; Boo Y C; Vega J D; Taylor W R; Jo H
AUTHOR ADDRESS: Department of BME, Georgia Tech and Emory University, 1639 Pierce Drive, Atlanta, GA, 30329, USA**USA
AUTHOR E-MAIL ADDRESS: gsoresc@emory.edu; gt0180e@prism.gatech.edu; dweiss2@emory.edu; gtg781d@mail.gatech.edu; nolan.boyd@bme.gatech.edu; yong.boo@bme.gatech.edu, jvega@emory.edu; wtaylor@emory.edu; hanjoong.jo@bme.gatech.edu
JOURNAL: FASEB Journal 17 (4-5): pAbstract No. 864.1 March 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: FASEB Meeting on Experimental Biology: Translating the Genome San Diego, CA, USA April 11-15, 2003: 20030411
SPONSOR: FASEB
ISSN: 0892-6638 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Laminar shear (LS) protects arterial walls from %%%atherosclerosis%%%, whereas unstable OS is considered to be pro-atherogenic. Here we examined the hypothesis that LS and OS prevents or initiates atherogenesis by changing expression profiles of endothelial genes and proteins. Through Gene Chip studies, we found that %%%BMP4%%% mRNA was inhibited by apprx4.5-fold in mouse aortic EC (MAEC) exposed to LS for 1 day. This was confirmed by real time PCR and Western blot analysis of MAEC. In contrast, OS increased %%%BMP4%%% protein expression by apprx2-fold. Immunohistochemistry of human coronary arteries with various levels of %%%atherosclerotic%%% lesions revealed that %%%BMP4%%% expression was significant only in EC overlying foam cells but not in other areas of EC. Since OS and LS are well known to stimulate and inhibit monocyte adhesion to EC, respectively, we examined whether %%%BMP4%%% mediates this key atherogenic event. We found that %%%BMP4%%% and OS stimulated monocyte adhesion by inducing ICAM-1 expression in EC, and both responses could be completely blocked by treating EC with noggin (%%%BMP4%%% inhibitor). In addition, treatment with an NFkB inhibitor (MG132) prevented ICAM-1 induction stimulated by either OS or %%%BMP4%%%, implicating a role of NFkB pathway. These results identify a novel paradigm of %%%BMP4%%% effect as an %%%inflammatory%%% cytokine in response to OS in EC. This %%%BMP4%%% effect may be responsible for the pro-atherogenic effects of OS.

2/7/20 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.
(c) 2008 The Thomson Corp. All rts. reserv.

0445266 DBR Accession No.: 2008-03465 PATENT
New monoclonal antibody that binds an epitope on human BMP2 or %%%BMP4%%%, useful for preparing a composition for treating or preventing a disease associated with abnormal bone formation and ossification - recombinant human bone morphogenetic protein epitope-specific monoclonal antibody produced by vector mediated gene expression in hybridoma, useful as vaccine for prevention of abnormal bone formation and ossification
AUTHOR: ZIMMERMAN D; SELBY M; SRINIVASAN M; BELL A; SINGH S; THEOLIS R ; LEBLANC H N; EMORY K D
PATENT ASSIGNEE: MEDAREX INC 2008
PATENT NUMBER: WO 200830611 PATENT DATE: 20080313 WPI ACCESSION NO.: 2008-D21739 (200823)
PRIORITY APPLIC. NO.: US 824596 APPLIC. DATE: 20060905
NATIONAL APPLIC. NO.: WO 2007US19652 APPLIC. DATE: 20070905
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A new isolated monoclonal antibody or its antigen binding portion, antibody fragment or antibody mimetic binds an epitope on human bone morphogenic protein 2 (BMP2) or %%%BMP4%%% recognized by an antibody comprising a heavy or light chain variable region comprising SEQ ID NO: 32 or 35. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are: (1) a composition comprising the isolated antibody and a pharmaceutically acceptable carrier; (2) an isolated nucleic acid molecule encoding the heavy or light chain of the isolated antibody; (3) an expression vector comprising the nucleic acid molecule; (4) a host cell comprising the expression vector; (5) a method for preparing an anti-BMP2 or anti-%%%BMP4%%% antibody; (6) a method for treating or preventing a disease associated with abnormal bone formation and ossification; (7) a hybridoma expressing the antibody; (8) a method of making the antibody; and (9) a method of making anti-BMP2 or anti-%%%BMP4%%% antibodies. BIOTECHNOLOGY - Preferred Antibody: The antibody is a full-length antibody of an IgG1, IgG2, IgG3 or IgG4 isotype. The antibody is a whole antibody, an antibody fragment, a humanized antibody, a single chain antibody, an immunoconjugate, a defucosylated antibody, or a bispecific antibody. The antibody fragment is a UniBody, a domain antibody or a Nanobody. The antibody mimetic is an Affibody, a DARPin, an Anticalin, an Avimer, a Versabody or a Duocalin. The immunoconjugate comprises a therapeutic agent. The therapeutic agent is a cytotoxin or a radioactive isotope. The antibody binds to human BMP2 or %%%BMP4%%% with a KD of 5.5 x 109 M or less. Preferred Method: Preparing an anti-BMP2 or anti-%%%BMP4%%% antibody comprises: (a) obtaining a host cell that contains one or more nucleic acid molecules encoding the antibody; (b) growing the host cell in a host cell culture; (c) providing host cell culture conditions where the one or more nucleic acid molecules are expressed; and (d)

recovering the antibody from the host cell or from the host cell culture. Treating or preventing a disease associated with abnormal bone formation and ossification comprises administering to a subject an anti-BMP2 or anti-%%%BMP4%%% antibody. The disease is fibrodysplasia ossificans progressiva (FOP), progressive osseous heterogenia, spinal cord injury, intramuscular hematoma, complications from orthopedic surgery, psoriatic arthritis, osteoarthritis, ankylosing spondylitis (AS), seronegative anthropathies, skeletal hyperostosis, otosclerosis, stapes ankylosis, bone cancer, prostate cancer, exotoses, %%%atherosclerosis%%%, valvular heart disease. The disease is a cancer consisting of bone cancer, prostate cancer, lung cancer, melanoma, hematopoietic cancer, renal cancer or breast cancer. Making the antibody comprises: (a) immunizing a transgenic animal comprising human immunoglobulin genes with a BMP2 or %%%BMP4%%% peptide; (b) recovering B-cells from the transgenic animal; (c) making hybridomas from the B-cells; (d) selecting hybridomas that express antibodies that bind BMP2 or %%%BMP4%%%, and (e) recovering the antibodies that bind BMP2 or %%%BMP4%%% from the selected hybridomas. Making anti-BMP2 or anti-%%%BMP4%%% antibodies comprises: (a) immunizing a transgenic animal comprising human immunoglobulin genes with a BMP2 or %%%BMP4%%% peptide; (b) recovering mRNA from the B cells of the transgenic animal; (c) converting the mRNA to cDNA, (d) expressing the cDNA in phages such that anti-BMP2 or anti-%%%BMP4%%% antibodies encoded by the cDNA are presented on the surface of the phages; (e) selecting phages that present anti-BMP2 or anti-%%%BMP4%%% antibodies; (f) recovering nucleic acid molecules from the selected phages that encode the anti-BMP2 or anti-%%%BMP4%%% immunoglobulins; and (g) expressing the recovered nucleic acid molecules in a host cell, and recovering antibodies from the host cell that bind BMP2 or %%%BMP4%%%. ACTIVITY - Osteopathic. No biological data given. MECHANISM OF ACTION - Vaccine. USE - The monoclonal antibody or its antigen binding portion, antibody fragment or antibody mimetic is useful for preparing a composition for treating or preventing a disease associated with abnormal bone formation and ossification (claimed). ADMINISTRATION - Dosage comprises 0.01 to 25 mg/kg body weight. The composition is administered via intravenous, intramuscular, subcutaneous, spinal or epidermal route. EXAMPLE - No suitable example given.(142 pages)

2/7/21 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.
(c) 2008 The Thomson Corp. All rts. reserv.

0438356 DBR Accession No.: 2007-24663 PATENT
Use of bone morphogenetic protein (BMP), e.g. BMP2 or %%%BMP4%%%, for preparing a medicament for treating beta-cell dysfunction, e.g. type 2 diabetes, glucose intolerance, insulin resistance, or metabolic syndrome - preparation of medicament comprising of bone morphogenetic protein useful for the treatment of beta-cell dysfunction associated disease
AUTHOR: EDLUND H; DAHL U; GOULLEY J
PATENT ASSIGNEE: BETAGENON AB 2007
PATENT NUMBER: WO 2007093451 PATENT DATE: 20070907 WPI ACCESSION NO.: 2007-739775 (200769)
PRIORITY APPLIC. NO.: US 831952 APPLIC. DATE: 20060720
NATIONAL APPLIC. NO.: WO 2007GB740 APPLIC. DATE: 20070302
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT. NOVELTY - Use of a BMP or a fragment, variant, fusion, or derivative, in the preparation of a medicament for treating beta-cell dysfunction, where the bone morphogenetic protein is selected from BMP2 or %%%BMP4%%%. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are: (1) a method of treatment of beta-cell dysfunction; (2) a combination product comprising: (a) a first agent comprising BMP or a fragment, variant, fusion, or derivative, and (b) a second agent with efficacy in the treatment of a disease or condition associated with beta-cell dysfunction or type 2 diabetes, where each of components (a) and (b) is formulated in admixture with a pharmaceutical adjuvant, diluent, or carrier; (3) a method of making a combination product; (4) a kit of parts comprising: (a) at least one of components above, together with (b) instructions to use that component in conjunction with the other component; (5) a transgenic non-human animal comprising beta-cells, which express abnormal levels of a BMP or receptor, where the BMP is selected from BMP2 or %%%BMP4%%%; (6) a method for identifying a candidate compound for the treatment of a beta-cell dysfunction; and (7) an in vitro method for making cells capable of producing insulin.BIOTECHNOLOGY - Preferred Bone Morphogenetic Protein: The medicament enhances glucose stimulated insulin secretion from beta-cells. It also enhances BMPR1a signaling in beta-cells. The medicament modulates the level and/or function of one or more intrinsic factors selected from BMPR1a, BMPRII, Smadl, Smad4, Smad7, Id1, Id2, Ipf1/PDXl, Glut2, Nkx6.1, HNF1a, PC2, PCI/3, GLP-1r, GIPr, GCK, Kir6.2, SUR1, Rab3d, Rab27a, Calpain10, Snap-25, Hif1a, or Evi-1. Preferably, the medicament increases expression and/or function of the intrinsic factors selected from BMPR1a, BMPRII, Smadl, Smad4, Smad7, Id1, Id2, Ipf1/PDXl, Glut2, Nkx6.1, HNF1a, PC2, PCI/3, GLP-1r, GIPr, GCK, Kir6.2, SUR1, Rab3d, Rab27a, Calpain10, Snap-25, or Hif1a. The medicament decreases expression and/or function of Evi-1. The BMP, or fragment, variant, fusion, or derivative is a recombinant polypeptide. The BMP is a mammalian BMP, preferably a human BMP. The BMP is %%%BMP4%%% comprising SEQ ID NO. 1; or BMP2 comprising SEQ ID NO. 2. The medicament comprises a fragment of a naturally occurring BMP, or variant, fusion, or derivative. The fragment comprises at least 10 contiguous amino acids from a BMP, e.g. at least 20-305 contiguous amino acids. It also comprises a variant of a BMP, where the variant BMP is a non-naturally occurring variant. The variant BMP is a chimeric BMP, where the chimeric BMP comprises amino acid sequences derived from BMP2 and/or %%%BMP4%%%. The variant BMP has an amino acid sequence, which has at least 45% identity with naturally occurring BMP or a fragment, e.g. at least 50-99% identity. The variant BMP is a variant of human BMP2 and/or %%%BMP4%%%. The medicament also comprises a fusion protein, where the fusion protein comprises a polypeptide selected from albumin and the Fc portion of an IgG molecule, and fragments. The BMP, or fragment, variant, fusion, or derivative, is linear or cyclic. It is also linked to a polymer, and is PEGylated. Preferred Method: Treating beta-cell dysfunction comprises the administration of an amount of a BMP, or a fragment, variant, fusion, or derivative, to a patient. Alternatively, treating beta-cell dysfunction comprises administration of a combination product, or a kit of parts, to a subject suffering from, or susceptible to, beta-cell dysfunction. Specifically, treating dysfunction of beta-cells in vitro comprises contacting the beta-cells with a BMP or a fragment, variant, fusion, or derivative, or a combination product above. Making a combination product comprises bringing a component (a) above into association with a component (b), above, thus rendering the two components for administration in conjunction with each other. Identifying a candidate compound for the treatment of a beta-cell dysfunction comprises administering a compound to be tested to a transgenic non-human animal and determining the effect of the test compound on beta-cell function. Determining the effect of the test compound on beta-cell function comprises assaying one or more of the following: (a) insulin expression; (b) glucose tolerance; (c) glucose stimulated insulin secretion; and/or (d) expression of an intrinsic factor selected from BMPR1a, BMPRII, Smad1, Smad4, Smad7, Id1, Id2, Ipf1/PDXl, Glut2, Nkx6.1, HNF1a, PC2, PCI/3, GLP-1r, GIPr, GCK, Kir6.2, SUR1, Rab3d, Rab27a, Calpain10, Snap-25, Hif1a, or Evi-1. In vitro method for making cells capable of producing insulin comprises contacting stem cells or progenitor cells with a BMP or a fragment, variant, fusion, or derivative, or a combination product above. The cells capable of producing insulin are beta-cells. The stem cells or progenitor cells are mammalian cells, preferably, human cells. The stem cells or progenitor cells are stem cells, where the stem cells are embryonic stem cells. The stem cells are also pancreas stem cells. It is also progenitor cells. Preferred Combination Product. The combination product comprises a pharmaceutical formulation including a first agent comprising a BMP or a fragment, variant, fusion, or derivative, a second agent with efficacy in the treatment of a disease or condition associated with beta-cell dysfunction or type 2 diabetes, and a pharmaceutical adjuvant, diluent, or carrier. It also comprises a kit of parts comprising: (a) a pharmaceutical formulation including a first agent comprising a BMP or a fragment, variant, fusion, or derivative, in admixture with a pharmaceutical adjuvant, diluent, or

carrier, and (b) a pharmaceutical formulation including a second agent with efficacy in the treatment of a disease or condition associated with beta-cell dysfunction or type 2 diabetes, in admixture with a pharmaceutical adjuvant, diluent, or carrier, where the components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other. The second agent is a treatment for type 2 diabetes or hypoinsulinemia. The second agent is selected from insulin, insulin secretagogues (such as sulfonylureas), metformin, peroxisome proliferator-activated receptor agonists (PPARs; such as thiazolidinediones), alpha-glucosidase inhibitors, GLP-1 receptor agonists, GIP receptor agonists, dipeptidyl peptidase IV (DPP-IV) inhibitors, and inhibitors of 11-beta hydroxysteroid dehydrogenase type 1. Preferably, it is GLP-1 or a biologically active fragment, variant, fusion, or derivative, selected from Exendin-4 (Exenatide; Byetta), Exenatide long acting release (LAR), Exenatide derivatives (such as ZP10 developed by Zealand Pharmaceuticals), native GLP-1, human GLP-1 derivatives (such as BIM51077), DPP-IV resistant GLP-1 analogues (e.g. LY315902 and LY30761 SR), long acting GLP-1 derivatives (such as NN2211), and complex proteins (such as the GLP-1-albumin complex CJC-1131). It is also a DPP-IV inhibitor selected from Vildagliptin (LAF237), MK-0431-Sitagliptin, or Saxagliptin. The second agent is also gastric inhibitory polypeptide (GIP), or a biologically active fragment, variant, fusion, or derivative. Preferred Transgenic Non-Human Animal: The transgenic non-human animal comprises beta-cells, which express increased levels of a BMP relative to corresponding non-transgenic non-human animals. The beta-cells comprise a bmp gene under the control of an Ipf1/Pdx1 promoter. It also comprises beta-cells, which express decreased levels of a BMP receptor relative to corresponding non-transgenic non-human animals, where the beta-cells comprise a dominant native, kinase-deficient from of the Bmpr1a gene under the control of an Ipf1/Pdx1 promoter. The animal is a rodent or a mouse. ACTIVITY - Antidiabetic; Metabolic; Antilipemic; Nephrotropic; Ophthalmological; Anorectic; Nephrotropic; Cardiovascular-Gen; Antiarteriosclerotic; Cerebroprotective; Vasotropic; Cytostatic; Antimicrobial; Antitubercular; Tuberculostatic. MECHANISM OF ACTION - BMP-Agonist; BMP-Antagonist. To assess whether repeated administration of %%%BMP4%%% protein could enhance glucose stimulated insulin secretion and improve glucose tolerance in response to Exendin-4, insulin secretion following glucose injection in CBA mice which had received twice daily intraperitoneal injections of 20 micrograms of %%%BMP4%%%/kg bodyweight for 3 days was examined. On day 4, the animals received a final intraperitoneal injection of %%%BMP4%%% and a single intraperitoneal injection of Exendin-4. %%%BMP4%%% in combination with Exendin-4 resulted in a significant stimulation of insulin secretion and a concomitant improvement in glucose tolerance compared to vehicle control and Exendin-4 alone. USE - The BMP or a fragment, variant, fusion, or derivative, is useful in the preparation of a medicament for treating beta-cell dysfunction. The medicament is for treating beta-cell dysfunction associated with a condition selected from type 2 diabetes, atypical forms of diabetes (such as latent autoimmune diabetes in adults (LADA) and Maturity-Onset Diabetes of Young (MODY)), glucose intolerance, insulin resistance, metabolic syndrome, dyslipidemia, hypercholesterolemia, high blood pressure, obesity, fatty liver conditions, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, cardiovascular disease, %%%atherosclerosis%%% , cerebrovascular conditions, stroke, cancer, or infectious diseases (such as tuberculosis). It is also for treating transplanted beta-cells. The combination product is useful in medicine. The combination product, kit, and methods are useful in the treatment of beta-cell dysfunction. The transgenic non-human animal is also useful in a method for identifying candidate compounds with efficacy in the treatment of beta-cell dysfunction (all claimed). ADMINISTRATION - Dosage is 1-1000 mg per adult, preferably 0.015-15 mg/kg. Administration can be through oral, buccal, sublingual, intravenous, intraarticular, intraarterial, intraperitoneal, intrathecal, intraventricular, intrasternal, intracranial, intramuscular, or subcutaneous route. EXAMPLE - No suitable example given.(102 pages)

2/7/22 (Item 3 from file: 357)

DIALOG(R)File 357:Derwent Biotech Res.
(c) 2008 The Thomson Corp. All rts. reserv.

0424820 DBR Accession No.: 2007-10758 PATENT

New multivalent and multispecific binding proteins, useful for preventing and/or treating acute and chronic %%%inflammatory%%% and other diseases - involving humanized antibody production, useful for an immunotherapy application

AUTHOR: WU C; GHAYUR T; DIXON R W; SALFELD J G

PATENT ASSIGNEE: WU C; GHAYUR T; DIXON R W; SALFELD J G 2007

PATENT NUMBER: US 20070071675 PATENT DATE: 20070329 WPI ACCESSION NO.: 2007-308401 (200730)

PRIORITY APPLIC. NO.: US 507050 APPLIC. DATE: 20060818

NATIONAL APPLIC. NO.: US 507050 APPLIC. DATE: 20060818

LANGUAGE: English

ABSTRACT: DERWENT ABSTRACT: NOVELTY - A binding protein comprising a polypeptide chain, where the polypeptide chain comprises VD1-(X1)nVD2-C-(X2)n, where VD1 is a first variable domain, VD2 is a second variable domain, C is a constant domain, X1 represents an amino acid or polypeptide, X2 represents an Fc region and n is 0 or 1, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are: (1) a binding protein conjugate comprising a binding protein above, the binding protein conjugate further comprising an agent selected from an immunoadhesion molecule, an imaging agent, a therapeutic agent, or a cytotoxic agent; (2) an isolated nucleic acid encoding a binding protein amino acid sequence above; (3) a vector comprising an isolated nucleic acid; (4) a host cell comprising a vector; (5) a method of producing a binding protein; (6) a pharmaceutical composition comprising the binding protein above and a pharmaceutical carrier; and (7) a method for treating a subject for a disease or a disorder. BIOTECHNOLOGY - Preferred Binding Protein: The VD1 and VD2 are heavy or light chain variable domains. The heavy or light chain variable domain is a murine heavy or light chain variable domain, a human heavy or light chain variable domain, a CDR grafted heavy or light chain variable domain, or a humanized heavy or light chain variable domain. VD1 and VD2 are capable of binding the same or different antigens. The C is a heavy chain constant domain, where X1 is a linker if X1 is not CH1, where the linker is selected from the following sequences: Ala-Lys-Thr-Thr-Pro-Lys-Leu-Glu-Glu-Gly-Glu-Phe-Ser-Glu-Ala-Arg; Ala-Ly s-Thr-Thr-Pro-Lys-Leu-Glu-Glu-Gly-Glu-Phe-Ser-Glu-Ala-Arg-Val; Ala-Lys-Thr-Thr-Pro-Lys-Leu-Glu-Gly; Ser-Ala-Lys-Thr-Thr-Pro-Lys-Leu-Glu-Gly; Ala-Lys-Thr-Thr-Pro-Lys-Leu-Glu-Glu-Gly-Glu-Phe-Ser-Glu-Ala-Arg-Val; Ser-Ala-Lys-Thr-Thr-Pro; Ser-Ala-Lys-Thr-Thr-Pro-Lys-Leu-Glu-Gly; Arg-Ala-Asp-Ala-Ala-Pro; Arg-Ala-Asp-Ala-Ala-Pro-Thr-Val-Ser; Arg-Ala-Asp-Ala-Ala-Ala-Gly-Gly-Pro-Gly-Ser; Arg-Ala-Asp-Ala-Ala-Ala-Ala(G4S)4; Ser-Ala-Lys-Thr-Thr-Pro; Ser-Ala-Lys-Thr-Thr-Pro-Lys-Leu-Glu-Gly; Ser-Ala-Lys-Thr-Thr-Pro-Lys-Leu-Glu-Glu-Gly-Glu-Phe-Ser-Glu-Ala-Arg-Val; Ala-Asp-Ala-Ala-Pro; Ala-Asp-Ala-Ala-Pro-Thr-Val-Ser-Ile-Phe-Pro-Pro; Thr-Val-Ala-Ala-Pro; Thr-Val-Ala-Ala-pro-Ser-Val-Phe-Ile-Phe-Pro-Pro; Gln-Pro-Lys-Ala-Ala-Pro; Gln-Pro-Lys-Ala-Ala-Pro-Ser-Val-Thr-Leu-Phe-Pro; Ala-Lys-Thr-Thr-Pro-Pro; Ala-Lys-Thr-Thr-Pro-Pro-Ser-Val-Thr-Pro-Leu-Ala-Pro; Ala-Lys-Thr-Thr-Ala-Pro; Ala-Lys-Thr-Thr-Ala-Pro-Ser-Val-Tyr-Pro-Leu-Ala-Pro; Ala-Ser-Thr-Lys-Gly-Pro; Ala-Ser-Thr-Lys-Gly-Pro-Ser-Val-Phe-Pro-Leu-Ala-Pro; Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser; Gly-Glu-Asn-Lys-Val-Glu-Tyr-Ala-Pro-Ala-Leu-Met-Ala-Leu-Ser; Gly-Pro-Ala-Lys-Glu-Leu-Thr-Pro-Lys-Lys-Glu-Ala-Lys-Val-Ser; or Gly-His-Glu-Ala-Ala-Ala-Val-Met-Gln-Val-Gln-Tyr-Pro-Ala-Ser. X2 is an Fc region. where the Fc region is a variant Fc region. The binding protein does not comprise X2. Specifically, a binding protein comprises a polypeptide chain, where the polypeptide chain comprises VD1-(X1)nVD2-C-(X2)n, where VD1 is a first heavy chain variable domain, VD2 is a second heavy chain variable domain, C is a heavy chain constant domain, X1 is a linker if it is not CH1, and X2 is an Fc region. Specifically, a binding protein comprises a polypeptide chain, where the polypeptide chain comprises VD1-(X1)nVD2-C-(X2)n, where VD1 is a first light chain variable domain, VD2 is a second light chain variable domain, C is a light chain constant domain, X1 is a linker if it is not CH1, and X2 does not comprise an Fc region. A binding protein comprises first and second polypeptide chains, where the first polypeptide chain comprises VD1-(X1)n-VD2-C-(X2)n, where VD1 is a first

heavy chain variable domain, VD2 is a second heavy chain variable domain, C is a heavy chain constant domain, X1 is a linker if it is not CH1, and X2 is an Fc region, and the second polypeptide chain comprises VD1(X1)n-VD2-C-(X2)n, where VD1 is a first light chain variable domain, VD2 is a second light chain variable domain, C is a light chain constant domain, X1 is a linker if it is not CH1, and X2 does not comprise an Fc region. A binding protein comprises four polypeptide chains, where two polypeptide chains comprise VD1-(X 1)n-VD2C-(X2)n, where VD1 is a first heavy chain variable domain, VD2 is a second heavy chain variable domain, C is a heavy chain constant domain, X1 is a linker if it is not CH1, and X2 is an Fc region; and two polypeptide chains comprise VD1-(X1)n-VD2-C-(X2)n, where VD1 is a first light chain variable domain, VD2 is a second light chain variable domain, C is a light chain constant domain. X1 is a linker if it is not CH1, and X2 does not comprise an Fc region. The binding protein is capable of binding one or more targets, where the target is ABCF1; ACVR1; ACVR1B; ACVR2; ACVR2B; ACVRL1; ADORA2A; Aggrecan; AGR2; AICDA; AIF1; AIG1; AKAP1; AKAP2; AMH; AMHR2; ANGPT1; ANGPT2; ANGPTL3; ANGPTL4; ANPEP; APC; APOC1; AR; AZGP1 (zinc-a-glycoprotein); B7.1; B7.2; BAD; BAFF; BAG1; BAI1; BCL2; BCL6; BDNF; BLNK; BLR1 (MDR15); Bly5; BMP1; BMP2; BMP3; BMP3B (GDF10); %%%BMP4%%%; BMP6; BMP8; BMPR1A; BMPR1B; BMPR2; BPAG1 (plectin); BRCA1; C19orf10 (IL27w); C3; C4A; C5; CSR1; CANT1; CASP1; CASP4; CAV1; CCBP2 (D6/JAB61); CCL1 (I-309); CCL11 (eotaxin); CCL13 (MCP-4); CCL15 (MIP-Id); CCL16 (HCC-4); CCL17 (TARC); CCL18 (PARC); CCL19 (MIP-3b); CCL2 (MCP-1); MCAF; CCL20 (MIP-3a); CCL21 (MIP-2); SLC; exodus-2; CCL22 (MDC/STC-1); CCL23 (MPIF-1); CCL24 (MPIF-2/eotaxin-2); CCL25 (TECK); CCL26 (eotaxin-3); CCL27 (CTACK/ILC); CCL28; CCL3 (MIP-1a); CCL4 (MIP-1b); CCL5 (RANTES); CCL7 (MCP-3); CCL8 (mcp-2); CCNA1; CCNA2; CCND1; CCNE1; CCNE2; CCR1 (CKR1/HM145); CCR2 (mcp-RB/RA); CCR3 (CKR3/ CMKBR3); CCR4; CCR5 (CMKBR5/ChemR13); CCR6 (CMKBR6/CKR-L3/STRL22/DRY6); CCR7 (CKR7/ EBI1); CCR8 (CMKBR8/TER1/CKR-L1); CCR9 (GPR-9-6); CCRL1 (VSHK1); CCRL2 (L-CCR); CD164; CD19; CD1C; CD20; CD200; CD-22; CD24; CD28; CD3; CD37; CD38; CD3E; CD3G; CD3Z; CD4; CD40; CD40L; CD44; CD45RB; CD52; CD69; CD72; CD74; CD79A; CD79B; CD8; CD80; CD81; CD83; CD86; CDH1 (E-cad, enn); CDH11; CDH12; CDH13; CDH18; CDH19; CDH20; CDH5; CDH7; CDH8; CDH9; CDK2; CDK3; CDK4; CDK5; CDK6; CDK7; CDK8; CDK9; CDKN1A (p21Wapl/Cipl); CDKN1B (p27Kipl); CDKN1C; CDKN2A (p16INK4a); CDKN2B; CDKN2C; CDKN3; CEBPB; CER1; CHGA; CHGB; Chitinase; CHST10; CKLFSF2; CKLFSF3; CKLFSF4; CKLFSF5; CKLFSF6; CKLFSF7; CKLFSF8; CLDN3; CLDN7 (claudin-7); CLN3; CLU (clusterin); CMKLR1; CMKOR1 (RDC1); CNR1; COL18A1; COL1A1; COL4A3; COL6A1; CR2; CRP; CSF1(M-CSF); CSF2 (GM-CSF); CSF3 (GCSF); CTLA4; CTNNB1 (b-catenin); CTSB (cathepsin B); CX3CL1 (SCYD1); CX3CR1 (V28); CXCL1 (GRO1); CXCL10 (IP-10); CXCL11 (I-TAC/IP-9); CXCL12 (SDF1); CXCL13; CXCL14; CXCL16; CXCL2 (GRO2); CXCL3 (GRO3); CXCL5 (ENA-78/LIX); CXCL6 (GCP-2); CXCL9 (MIG); CXCR3 (GPR9/CKR-L2); CXCR4; CXCR6 (TYMSTR/ STRL33/Bonzo); CYB5; CYC1; CYSLTR1; DAB2IP; DES; DKFZp451J0118; DNCL1; DPP4; E2F1; ECGF1; EDG1; EFNA1; EFNA3; EFNB2; EGF; EGFR; ELAC2; ENG; ENO1; ENO2; ENO3; EPHB4; EPO; ERBB2 (Her2); EREG; ERK8; ESR1; ESR2; F3 (TF); FADD; FasL; FASN; FCER1A; FCER2; FCGR3A; FGF; FGF1 (aFGF); FGF10; FGF11; FGF12; FGF12B; FGF13; FGF14; FGF16; FGF17; FGF18; FGF19; FGF2 (bFGF); FGF20; FGF21; FGF22; FGF23; FGF3 (int-2); FGF4 (HST); FGF5; FGF6 (HST-2); FGF7 (KGF); FGF8; FGF9; FGFR3; FIGF (VEGFD); FIL1 (EPSILON); FIL1 (ZETA); FLJ12584; FLJ25530; FLRT1 (fibronectin); FLT1; FOS; FOSL1 (FRA1); FY (DARC); GAB RP (GABAa); GAGEB1; GAGEC1; GALNAC4S-6ST; GATA3; GDF5; GFI1; GGT1; GM-CSF; GNAS1; GNRH1; GPR2 (CCR10); GPR31; GPR44; GPR81 (FKSG80); GRCC10 (C10); GRP; GSN (Gelsolin); GSTP1; HAVCR2; HDAC4; HDAC5; HDAC7A; HDAC9; HGF; HIF1A; HIP1; histamine and histamine receptors; HLA-A; HLA-DRA; HM74; HMOX1; HUMCYT2A; ICEBERG; ICOSL; ID2; IFN-A; IFNA1; IFNA2; IFNA4; IFNA5; IFNA6; IFNA7; IFNB1; IFNgamma; IFNW1; IGBP1; IGF1; IGF1R; IGF2; IGFBP2; IGFBP3; IGFBP6; IL-1; IL10; IL10RA; IL10RB; IL11; IL11RA; IL12; IL12A; IL12B; IL12RB1; IL12RB2; IL13; IL13RA1; IL13RA2; IL14; IL15; IL15RA; IL16; IL17; IL17B; IL17C; IL17R; IL18; IL18BP; IL18R1; IL18RAP; IL19; IL1A; IL1B; IL1F10; IL1F5; IL1F6; IL1F7; IL1F8; IL1F9; IL1HY1; IL1R1; IL1R2; IL1RAP; IL1RAP.1; IL1RAPL2; IL1RL1; IL1RL2 IL1RN; IL2; IL20; IL20RA; IL21R; IL22; IL22R; IL22RA2; IL23; IL24; IL25; IL26; IL27; IL29A; IL28B; IL29; IL2RA; IL2RB; IL2RG; IL3; IL30; IL3RA; IL4; IL4R; IL5; IL5RA; IL6; IL6R; IL6ST (glycoprotein 130); IL7; IL7R; IL8; IL8RA; IL8RB; IL8RB; IL9; IL9R; ILK; INHA; INHBA; INSL3; INSL4; IRAK1; IRAK2; ITGA1; ITGA2; ITGA3; ITGA6 (a6 integrin); ITGAV; ITGB3; ITGB4 (b 4 integrin); JAG1; JAK1; JAK3; JUN; K6HF; KAI1; KDR; KIT/LG; KLF5 (GC Box BP); KLF6; KLK10; KLK12; KLK13; KLK14; KLK15; KLK3; KLK4; KLK5; KLK6; KLK9; KRT 1; KRT 19 (Keratin 19); KRT2A; KRTHB6 (hair-specific type II keratin); LAMA5; LEP (leptin); Lingo-p75; Lingo-Troy; LPS; LTA (TNF-b); LTB; LTBP4 (GPR16); LTB4R2; LTBR; MACMARCKS; MAG or Omgp; MAP2K7 (c-Jun); MDK; MIB1; midkine; MIF; MIP-2; MKI67 (Ki-67); MMP2, MMP9; MS4A1; MSMB; MT3 (metallothionectin-III); MTSS1; MUC1 (mucin); MYC; MYD88; NCK2; neurocan; NFKB1; NFKB2; NGFB (NGF); NGFR; NgR-Lingo; NgR-Nogo66 (Nogo); NgRp75; NgR-Troy; NME1 (NM23A); NOX5; NPPB; NROB1; NROB2; NR1D1; NR1D2; NR1H2; NR1H3; NR1H4; NR1I2; NR1I3; NR2C1; NR2C2; NR2E1; NR2E3; NR2F1; NR2F2; NR2F6; NR3C1; NR3C2; NR4A1; NR4A2; NR4A3; NR5A1; NR5A2; NR6A1; NRP1; NRP2; NT5E; NTN4; ODZ1; OPRD1; P2RX7; PAP; PART1; PATE; PAWR; PCA3; PCNA; PDGFA; PDGFB; PECAM1; PF4 (CXCL4); PGF; PGR; phosphacan; PIAS2; PIK3CG; PLAU (uPA); PLG; PLXDC1; PPBP (CXCL7); PPID; PR1; PRKCQ; PRKD1; PRL; PROC; PROK2; PSAP; PSCA; PTAFR, PTEN; PTGS2 (COX-2); PTN; RAC2 (p21Rac2); RARB; RGS1; RGS13; RGS3; RNFII0 (ZNF144); ROBO2; S100A2; SCGB1D2 (lipophilin B); SCGB2A1 (mammaglobin 2); SCGB2A2 (mammaglobin 1); SCYE1 (endothelial Monocyte-activating cytokine); SDF2; SERPINA1; SERPINA3; SERPINB5 (maspin); SERPINE1 (PAI-1); SERPINF1; SHBG; SLA2; SLC2A2; SLC33A1; SLC43A1; SLIT2; SPP1; SPRR1B (Spr1); ST6GAL1; STAB1; STAT6; STEAP; STEAP2; TB4R2; TBX21; TCP 10; TDGF1; TEK; TGFA; TGFB 1I; TGFB 111; TGFB1; TGFB2; TGFB3; TGFB1; TGFBR2; TGFBR3; TH1L; THBS1 (thrombospondin-1); THBS2; THBS4; THPO; TIE (Tie-l); TIMP3; tissue factor; TLR10; TLR2; TLR3; TLR4; TLR5; TLR6; TLR7; TLR8; TLR9; TNF; TNF-alpha; TNFAIP2 (B94); TNFAIP3; TNFRSF1A; TNFRSF1A; TNFRSF1B; TNFRSF21; TNFRSF25; TNFRSF6; TNFRSF6B; TNFRSF7; TNFRSF8; TNFRSF9; TNFSF10 (TRAIL); TNFSF11 (TRANCE); TNFSF12 (APO3L); TNFSF13 (April); TNFSF13B; TNFSF14 (HVEM-L); TNFSF15 (VEGI); TNFSF18; TNFSF4 (OX40 ligand); TNFSF5 (CD40 ligand); TNFSF6 (FasL); TNFSF7 (CD27 ligand); TNFSF8 (CD30 ligand); TNFSF9 (4-1BB ligand); TOLLIP; Toll-like receptors; TOP2A (topoisomerase Ila); TP53; TPI1; TPM2; TRADD; TRAF1; TRAF2; TRAF3; TRAF4; TRAF5; TRAF6; TREM1; TREM2; TRPC6; TSLP; TWEAK; VEGF; VEGFB; VEGFC; versican; VHL; VLA-4; XCL1 (lymphotactin); XCL2 (SCM-1b). XCR1 (GPR5/ CCXCR1); YY1; or ZFPM2. The binding protein is capable of binding a two targets, where the two targets are selected from CD138 and CD20; CD138 and CD40; CD20 and CD3; CD38 and CD138; CD38 and CD20; CD38 and CD40; CD40 and CD20; CD19 and CD20; CD-8 and IL-6; PDL-1 and CTLA-4; CTLA-4 and BTNO2; CSPGs and RGM A; IGF1 and IGF2; IGF1/2 and Erb2B; IL-12 and IL-18; IL-12 and TWEAK; IL-13 and ADAM8; IL-13 and CL25; IL-13 and IL-1beta; IL-13 and IL-25; IL-13 and IL-4; IL-13 and IL-9; IL-13 and LHR agonist; IL-13 and MDC; IL-13 and MIF; IL-13 and PED2; IL-13 and SPRR2a; IL-13 and SPRR2b; IL-13 and TARC; IL-13 and TGF-beta 1; IL-17 and IL-23; IL-6 and RGM A; NgR and RGM A; NogoA and RGM A; OMGp and RGM A; RGM A and RGM B; Te38 and TNFalpha; TNFalpha and IL-12; TNFalpha and IL-12p40; TNFalpha and IL-13; TNFalpha and IL-15; TNFalpha and IL-17; TNFalpha and IL-18; TNFalpha and IL-1beta; TNFalpha and IL-23; TNFalpha and MIF; TNFalpha and PEG2; TNFalpha and PGE4; TNFalpha and VEGF; and VEGFR and EGFR; TNFalpha and RANK ligand; TNFalpha and Blys; TNFalpha and GP130; TNFalpha and CD-22; and TNFalpha and CTLA-4, where the binding protein is capable of modulating a biological function of one or more targets, or neutralizing one or more targets. The target is cytokine, chemokine, cell surface protein, enzyme, or receptor. The cytokine is selected from lymphokines, monokines, or polypeptide hormones, where the cytokines are IL-1alpha and IL-1beta, where the binding protein comprises a DVD heavy chain amino acid sequence selected from SEQ ID NOS: 33, 37, 41, 45, 47, 51, 53, 55, 57, or 59, and a DVD light chain amino acid sequence selected from SEQ ID NOS: 35, 39, 43, 46, 49, 52, 54, 56, 58, or 60. The cytokines are TNF-alpha and IL-13. The cytokines are IL-12 and IL-18, where the binding protein comprises a DVD heavy chain amino acid sequence selected from SEQ ID NOS: 83, 90, 93, 95, or 114; and a DVD light chain amino acid sequence selected from SEQ ID NOS: 86, 91, 94, 96, or 116. The chemokine is CCR2, CCR5, or CXCL- 13. The cell surface protein is an integrin. The cell surface proteins are CD-20 and CD3, where the binding protein comprises a DVD heavy chain amino acid sequence is SEQ ID NO: 97, and a DVD light chain SEQ ID NO. 101. The enzyme is selected from kinases or proteases. The receptor is lymphokine receptor, monokine receptor, or polypeptide hormone receptor. The binding protein has an on rate constant (Kon) to the one

or more targets selected from at least 102 to 106M-1s-1, as measured by surface plasmon resonance. The binding protein has an off rate constant (Koff) to the one or more targets selected from at most 10-6 to 10-3s-1, as measured by surface plasmon resonance. The binding protein has a dissociation constant (KD) to the one or more targets selected from at most 10-13 to 10-7 M. Preferred Binding Protein Conjugate: The agent is an imaging agent selected from a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, or biotin. The imaging agent is a radiolabel selected from 3H, 14C, 35S, 90Y, 99Tc, 111In, 125I, 131I, 177Lu, 166Ho, or 153Sm. The agent is a therapeutic or cytotoxic agent selected from an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, or an apoptotic agent. The binding protein is a crystallized binding protein, where the crystal is a carrier-free pharmaceutical controlled release crystal, where the binding protein has a greater half life in vivo than the soluble counterpart of the binding protein, and where the binding protein retains biological activity. Preferred Vector: The vector is pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pcDNA3.1 TOPO, pEF6 TOPO, or pBJ. Preferred Host Cell: The host cell is a prokaryotic cell, where the host cell is E. coli. The host cell is a eukaryotic cell, where the eukaryotic cell is protist cell, animal cell, plant cell, or fungal cell. The eukaryotic cell is an animal cell selected from a mammalian cell, an avian cell, or an insect cell. The host cell is a CHO cell or COS. The host cell is a yeast cell, where the yeast cell is Saccharomyces cerevisiae. The host cell is an insect Sf9 cell. Preparation (claimed): Producing a binding protein comprises culturing a host cell of (4) in culture medium under conditions to produce the binding protein. 50%-95% of the binding protein produced is a dual specific tetravalent binding protein. Preferred Method: Treating a subject for a disease or a disorder by administering to the subject the binding protein above such that treatment is achieved. Preferred Pharmaceutical Composition: The pharmaceutical composition further comprises at least one additional therapeutic agent selected from therapeutic agent, imaging agent, cytotoxic agent, angiogenesis inhibitors; kinase inhibitors; co-stimulation molecule blockers; adhesion molecule blockers; anti-cytokine antibody or functional fragment thereof; methotrexate; cyclosporin; rapamycin; FK506; detectable label or reporter; a TNF antagonist; an antirheumatic; a muscle relaxant, a narcotic, a non-steroid anti-%%%inflammatory%%% drug (NTHE), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosupressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist. ACTIVITY - Antirheumatic; Antiarthritic; Osteopathic; Dermatological; Antiinflammatory; Immunosuppressive; Antiulcer; Gastrointestinal-Gen; Antidiabetic; Antiasthmatic; Antiallergic; Antipsoriatic; Antiarteriosclerotic; Nephrotropic; Hepatotropic; Antibacterial; Antimicrobial; Anti-HIV; Anticonvulsant; Antiparkinsonian; Neuroprotective; Nootropic; Cerebroprotective; Vasotropic; Antianemic; Cardiant; Respiratory-Gen; Antiinfertility; Cytostatic. No biological data given. MECHANISM OF ACTION - Gene Therapy. USE - The binding protein and method are useful for treating a disorder, e.g. rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, ulcerative colitis, %%%inflammatory%%% bowel disease, insulin dependent diabetes mellitus, thyroditis, asthma, allergic diseases, psoriasis, graft versus host disease, %%%atherosclerosis%%%, nephrotic syndrome, microscopic vasculitis of the kidneys, chronic active hepatitis, toxic shock syndrome, sepsis syndrome, infectious diseases, AIDS, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, hemolytic anemia, heart failure, myocardial infarction, adult (acute) respiratory distress syndrome, atopic allergy, autoimmune bullous disease, pemphigus vulgaris, autoimmune hemolytic anemia, Hepatitis B, Hepatitis C, female infertility, vasculitic diffuse lung disease, fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, osteoarthrosis, autoimmune neutropenia, renal disease NOS, glomerulonephritides, pulmonary hypertension secondary to connective tissue disease, rheumatoid spondylitis, autoimmune thrombocytopenia, idiopathic thrombocytopenia, autoimmune thyroid disease, hyperthyroidism, atrophic autoimmune hypothyroidism, chronic liver diseases, allergy and asthma, mental disorders, and cancers; and hematopoietic malignancies, acute and chronic parasitic or infectious processes, acute or chronic bacterial infection, acute pancreatitis, acute renal failure, adenocarcinomas, aerial ectopic beats, AIDS dementia complex, anemia, angina pectoris, arteriosclerosis, Burns, cardiomyopathy, cardiopulmonary bypass %%%inflammation%%% response, chronic obstructive pulmonary disease (COPD), congestive heart failure, cystic fibrosis, dengue hemorrhagic fever, dermatitis, diabetes, hypertension, kidney transplant rejection, liver transplant rejection, malaria, myasthenia gravis, nephritis, nephrosis, neurodegenerative diseases, Non-Hodgkins lymphoma, organomegaly, osteoporosis, peripheral %%%vascular%%% disorders, peritonitis, pernicious anemia, pneumonia, endocrinopathy, preeclampsia, restrictive cardiomyopathy, sarcomas, scleroderma, senile chorea, seronegative arthropathies, shock, sickle cell anemia, skin allograft rejection, skin changes syndrome, small bowel transplant rejection, xenograft rejection of any organ or tissue. ADMINISTRATION - Administration is by parenteral, subcutaneous, intramuscular, intravenous, intraarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means (claimed). No dosage details given. ADVANTAGE - The present invention provides improved multivalent binding proteins capable of binding two or more antigens. EXAMPLE - Parent mAbs including two high affinity murine Abs, antiIE-1alpha (clone 3D12.E3) and anti-hIE-1beta (clone 13F5.G5), were obtained by immunizing Balb/c mice with recombinant IL-1alpha protein (rML-1alpha) and recombinant IL-1beta protein (rhIL-1beta), respectively. The VL/VR genes of these two hybridoma clones were isolated by RT-PCR using the mouse Ig Primer Kit. The VL/VR genes were first converted into chimeric antibodies (with human constant regions) to confirm activity and potency. To genDVD1-Ig, the VR and VL of 13F5.G5 were directly fused to the N-terminus of the VR and VL of 3D12.E3, respectively. The DVD2-Ig was constructed similarly, except that it had a linker between the two variable domains in both the light chain (the linker sequence is ADAAP) and the heavy chain (the linker sequence is AKTTPP). These sequences were selected from the N-termini of murine Ck and CR1 sequences. These linker sequences, selected from the N-termini of murine Ck and CR1, are natural extension of the variable domains and exhibit a flexible conformation without significant secondary structures based on the analysis of several Fab crystal structures.(126 pages)

0399601 DBR Accession No.: 2006-13097
Thrombin and NAD(P)H oxidase-mediated regulation of CD44 and %%%BMP4%%%-Id pathway in VSMC, restenosis, and %%%atherosclerosis%%% - vascular smooth muscle cell CD44 and %%%BMP4%%%-Id pathway regulation analysis using cDNA microarray analysis for molecular therapy development
AUTHOR: VENDROV AE; MADAMANCHI NR; HAKIM ZS, ROJAS M, RUNGE MS
CORPORATE AFFILIATE: Univ N Carolina
CORPORATE SOURCE: Runge MS, Univ N Carolina, Dept Med, Cardiovasc Biol Ctr, 3033 OCB, Chapel Hill, NC 27599 USA
JOURNAL: CIRCULATION RESEARCH (98, 10, 1254-1263) 2006
ISSN: 0009-7330
LANGUAGE: English
ABSTRACT: AUTHOR ABSTRACT - To characterize novel signaling pathways that underlie NAD(P) H oxidase - mediated signaling in %%%atherosclerosis%%%, we first examined differences in thrombin-induced gene expression

between wild-type and p47phox(-/-) (NAD[P] H oxidase - deficient) VSMC. Of the 9000 genes analyzed by cDNA microarray method at the G(1)/S transition point. 76 genes were similarly and significantly modulated in both the cell types, whereas another 22 genes that encompass various functional groups were regulated in NAD(P) H oxidase - dependent manner. Among these 22 genes, thrombin-induced NAD(P) H oxidase - mediated regulation of Klf15, Igbp1, Ak4, Adamts5, Ech1, Serp1, Sec61a2, Aox1, Aoh1, Fxyd5, Rai14, and Serpinh1 was shown for the first time in VSMC. The role of NAD(P) H oxidase in the regulation of a subset of these genes (CD44, %%%BMP4%%%, Id1, and Id3) was confirmed using modulators of reactive oxygen species (ROS) generation, a ROS scavenger and in gain-of-function experiments. We then characterized regulation of these genes in restenosis and %%%atherosclerosis%%% . In both apoE(-/-) mice and in a mouse vascular injury model, these genes are regulated in NAD(P) H oxidase - dependent manner during vascular lesion formation. Based on these findings, we propose that NAD(P) H oxidase - dependent gene expression in general, and the CD44 and %%%BMP4%%%-Id signaling pathway in particular, is important in restenosis and %%%atherosclerosis%%%. (10 pages)

2/7/24 (Item 5 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.
(c) 2008 The Thomson Corp. All rts. reserv.

0375005 DBR Accession No.: 2005-20711 PATENT
Novel isolated polypeptide comprising human cleaved collagen triple helix repeat containing 1 (CTHRC1) or isolated mutant CTHRC1 polypeptide, useful for treating or preventing disease mediated by collagen matrix production e.g. fibrosis - vector-mediated gene transfer and expression in host cell for recombinant production production and transgenic animal for use in disease therapy
AUTHOR: LINDNER V
PATENT ASSIGNEE: MAINE MEDICAL CENT RES INST 2005
PATENT NUMBER: US 20050147602 PATENT DATE: 20050707 WPI ACCESSION NO.: 2005-479078 (200548)
PRIORITY APPLIC. NO.: US 939233 APPLIC. DATE: 20040910
NATIONAL APPLIC. NO.: US 939233 APPLIC. DATE: 20040910
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated polypeptide (I) comprising a human cleaved collagen triple helix repeat containing 1 (CTHRC1) or an isolated mutant CTHRC1 polypeptide (II) comprising substitution of a human CTHRC1 collagen domain with a mouse collagen 1 alpha 1 collagen domain, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) an isolated nucleic acid (III) encoding a human cleaved CTHRC1; (2) a vector (IV) comprising (III); (3) an isolated nucleic acid (V) complementary to (III), the complementary nucleic acid being in an antisense orientation; (4) a recombinant cell (VI) comprising (III), (IV) or (V); (5) an antibody (VII) that specifically binds with (I); (6) a composition (C1) comprising (V), (I) or (III), and a carrier; (7) a transgenic non-human mammal comprising (III); (8) kit (K1) for testing or preventing disease mediated by collagen production, comprising effective amount of CTHRC1, an applicator and an instruction material; (9) an isolated nucleic acid (VIII) encoding (III), comprising a nucleotide sequence in which the sequence encoding a human CTHRC1 collagen domain is replaced by a nucleotide sequence of mouse collagen 1 alpha 1; (10) increasing the level of BMP1 or BMP1 mRNA in a cell, involves contacting a cell expressing BMP1 with a CTHRC1 inhibitor; (11) identifying (M1) a compound that affects collagen production in a cell, involves contacting a cell comprising CTHRC1 with a test compound and assessing the level of CTHRC1 in the cell, where a higher or lower level CTHRC1 in the cell contacted with the test compound compared with the level of CTHRC1 in a second otherwise identical cell not contacted with the test compound is an indication that the test compound inhibits collagen production in the cell, thus identifying a compound that inhibits collagen production in the cell; (12) a compound (C2) identified by (M1); (13) increasing bone matrix production in a cell or collagen production in a mammal, involves administering an effective amount of an inhibitor of CTHRC1 to the cell or mammal; (14) a kit (K2) for decreasing the level of BMP1 or BMP1 mRNA in a cell, increasing the level of a propeptide in a cell, inhibiting collagen formation by a cell, decreasing bone matrix formation by a cell, or decreasing the level of collagen in a cell, comprising a BMP1 inhibiting amount of CTHRC1, an applicator and instruction material for use; (15) a kit (K3) for increasing the level of a BMP1 in a cell, comprising CTHRC1 inhibitor, an applicator and instruction material for use;(16) increasing the level of OPN in a cell, involves contacting the cell with a CTHRC1 inhibiting amount of a CTHRC1 inhibitor; (17) identifying (M2) a compound that effects a CTHRC1-mediated reduction of %%%BMP4%%% in a cell, involves contacting a CTHRC1-containing cell with a test compound, where a lower level of %%%BMP4%%% in the cell contacted with the test compound compared with the level of %%%BMP4%%% in a second otherwise identical cell not contacted with the test compound is an indication that the test compound reduces the level of %%%BMP4%%% in the cell, and further where the test compound affects the activity of CTHRC1; (18) treating (M3) a disease mediated by %%%BMP4%%% in a mammal in need, involves administering to a mammal afflicted with a disease mediated by %%%BMP4%%% a CTHRC1 inhibiting amount of a CTHRC1 inhibitor; and (19) a kit (K4) for increasing the level of bone morphogenetic protein 4 (%%%BMP4%%%) in a cell, comprising an amount of CTHRC1 sufficient to increase the level of the %%%BMP4%%% in the cell, an applicator, and an instructional material for the use. BIOTECHNOLOGY - Preferred Polypeptide: (I) shares at least about 6% sequence identity with an amino acids sequence chosen from a fully defined 170 or 164 amino acid (SEQ ID No. 11 or 13) sequence given in the specification. In (II), the amino acids sequence of the human CTHRC1 collagen domain and the amino acid sequence of mouse collagen 1 alpha 1 collagen domain comprises a fully defined 34 amino acid (SEQ ID No. 14 and 15) sequence given in the specification, respectively. Preferred Nucleic Acid: (III) shares at least about 33% sequence identity with a nucleic acid sequence of cleaved CTHRC1 longer fragment comprising a fully defined 513 base pair (SEQ ID No. 10) sequence given in the specification or human cleaved CTHRC1 shorter fragment comprising a fully defined 495 base pair (SEQ ID No. 12) sequence given in the specification; and the encoded amino acid sequence shares at least about 33% sequence identity with SEQ ID No. 11 and 13. (III) further comprises a nucleic acid encoding a tag polypeptide covalently linked to it. The tag polypeptide is chosen from green fluorescent protein (GFP) tag polypeptide, an influenza virus hemagglutinin tag polypeptide, a myc tag polypeptide, a glutathione-S-transferase tag polypeptide, a myc-pyruvate kinase tag polypeptide, a His6 tag polypeptide, a FLAG tag polypeptide, and a maltose binding protein tag polypeptide. (III) further comprises a nucleic acid specifying a promoter/regulatory sequence operably linked to it. (V) shares at least about 33% identity with a nucleic acid complementary to (III). In (VIII), the nucleotide sequence encoding human CTHRC1 collagen domain and mouse collagen 1 alpha 1 comprises a fully defined 102 base pair (SEQ ID No. 15 and 17) sequence given in the specification, respectively. Preferred Vector: (IV) further comprises a nucleic acid specifying a promoter/regulatory sequence operably linked to it. Preferred Antibody: (VII) is chosen from a polyclonal, monoclonal, humanized, chimeric and synthetic antibody. Preferred Kit: The collagen is type I collagen. ACTIVITY - Vulnerary; Antiinflammatory; Respiratory-Gen.; Vasotropic. MECHANISM OF ACTION - CTHRC1 modulator (claimed). No supporting data is given. USE - (I)-(III) is useful for treating or preventing a disease mediated by collagen matrix production in a human, which involves administering to a human afflicted with the disease an effective amount of CTHRC1, where the diseases chosen from fibrosis, constrictive remodeling and restenosis. The fibrosis is of one or more organs chosen from kidney, lung, liver and skin. (I) or (II) is useful for decreasing level of bone morphogenetic protein 1 (BMP1) or BMP1 mRNA in a cell, increasing the level of a propeptide (chosen from procollagen and a propeptide of lysyl-oxidase) in a cell, inhibiting collagen formation by a cell, decreasing bone matrix formation by a cell, decreasing the level of collagen in a cell, increasing the level of procollagen in a cell, decreasing collagen formation in a mammal having a condition mediated by collagen formation, where the condition is chosen from wound scarring, wound healing, keloid formation, %%%inflammation%%% -associated scarring, pulmonary fibrosis, and angioplasty-associated

%%%vascular%%% fibrosis, or increasing the level of chordin in a cell, which involves contacting the cell with (I) or (II). (I) is useful for inhibiting cross-linking of collagen fibrils in a cell, which involves contacting a cell with a BMP1 inhibiting amount of (I) or (II), where BMP1 is responsible for processing a propeptide lysyl-oxidase, and further where the lysyl-oxidase mediates cross-linking of the collagen fibrils, thus inhibiting cross-linking of collagen fibrils in the cell.

(I) is useful for treating a disease mediated by expression of BMP1 in a mammal, increasing the level of bone morphogenetic protein 4 (%%%BMP4%%%) in a cell, increasing the level of %%%BMP4%%% promoter activity in a cell, promoting bone growth in a mammal, promoting differentiation of a stem cell, decreasing the level of osteopontin (OPN) in a cell, treating a disease mediated by under expression of %%%BMP4%%% in a mammal in need, and increasing the level of a muscle segment homeobox 1 (Msx1) in a cell. (K1) is useful for treating or preventing a disease mediator by collagen matrix production, where the disease is chosen from fibrosis, constrictive remodeling, arterial restenosis and vessel injury. (V) or (VII) is useful for inhibiting plaque rupture in a blood vessel, which involves administering a collagen matrix production enhancing amount of a CTHRC1 inhibitor chosen from (V) or (VII) to a blood vessel comprising a plaque, thus inhibiting plaque rupture in the blood vessel. (K2) is useful for decreasing the level of BMP1 or BMP1 mRNA in a cell, increasing the level of a propeptide in a cell, inhibiting collagen formation by a cell, decreasing bone matrix formation by a cell, or decreasing the level of collagen in a cell. (K3) is useful for increasing the level of a BMP1 in a cell. (M3) is useful for treating a disease mediated by %%%BMP4%%% in a mammal in need. (K4) is useful for increasing the level of bone morphogenetic protein 4 (%%%BMP4%%%) in a cell (all claimed).(115 pages)

2/7/25 (Item 6 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.
(c) 2008 The Thomson Corp. All rts. reserv.

0370317 DBR Accession No.: 2005-16023 PATENT
New stem cell comprising a self-replicating artificial chromosome comprising a neocentromere having centromeric chromatin domains, useful for tissue repair, replacement, rejuvenation and/or augmentation therapy - self-replicating artificial chromosome-containing stem cell for cell therapy and gene therapy
AUTHOR: CHOO K A; WONG L H; SAFFERY R E
PATENT ASSIGNEE: MURDOCH CHILDRENS RES INST 2005
PATENT NUMBER: WO 200540391 PATENT DATE: 20050506 WPI ACCESSION NO.: 2005-322966 (200533)
PRIORITY APPLIC. NO.: AU 2003905894 APPLIC. DATE: 20031027
NATIONAL APPLIC. NO.: WO 2004AU1469 APPLIC. DATE: 20041025
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A stem cell comprising a self-replicating artificial chromosome comprising a neocentromere having centromeric chromatin domains, where the artificial chromosome comprises expressible genetic material within the centromeric chromatin domains or in a region proximal thereto which modifies or introduces at least one trait in the stem cell, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a method of modulating the genetic potential of a stem cell; (2) a method for directing differentiation, proliferation or self-renewal of a stem cell; (3) a method for altering the genetic potential of a stem cell or its daughter cell; (4) an isolated nucleic acid molecule comprising a nucleotide sequence corresponding to a neocentromeric region of human DNA and having a centromeric chromatin domain, the nucleic acid molecule further comprising a second nucleic acid molecule inserted within the centromere chromatin domain or immediately adjoining or proximal region and which second nucleic acid molecule is expressible and where the expression product alters the genetic potential of a stem cell or its daughter cells where the neocentromeric region comprises a q and p arm domain, CENP-H, HP1 domain and a scaffold domain and comprises a gene selected from but not limited to hCG41809, hCG40976, hCG1811152, hCG1781464, hCG39839, hCG1781461, hCG40945, hCG1818126, hCG1811159, hCG409445 hCG40949, hCG39837, hCG40963, hCG40964, (5) a method differentiating a stem cell; and (6) a method of treating a subject therapeutically or prophylactically. BIOTECHNOLOGY - Preferred Stem Cell: The stem cell is selected from embryonic stem cells, somatic stem cells, germ stem cells, epidermal stem cells, adult neural stem cells, keratinocyte stem cells, melanocyte stem cells, adult renal stem cells, embryonic renal epithelial stem cells, embryonic endodermal stem cells, hepatocyte stem cells, mammary epithelial stem cells, bone marrow-derived stem cells, skeletal muscle stem cells, bone marrow mesenchymal stem cells, CD34+ hematopoietic stem cells, mesenchymal stem cells. The stem cell differentiates into a cell selected from keratinocytes, fibroblasts, pancreatic islets, pancreatic beta cells, kidney epithelial cells, hepatocytes, bile duct epithelial cells, lung fibroblasts, bronchial epithelial cells, alveolar type II pneumocytes, cardiomyocytes, simple squamous epithelial cells, descending aortic endothelial cells, aortic arch endothelial cells, aortic smooth muscle cells, corneal epithelial cells, osteoblasts, peripheral blood mononuclear progenitor cells, osteoclasts, stromal cells, splenic precursor cells, splenocytes, CD4+ T-cells, CD8+ T-cells, NK cell, monocytes, macrophages, dendritic cells, B-cells, goblet cells, pseudostriated ciliated columnar cells, pseudostratified ciliated epithelium, stratified epithelial cells, ciliated columnar cells, basal cells, cricopharyngeus muscle cells. The genetic material corresponds to a DNA sequence encoding a cytokine, growth factor or receptor selected from Activin RIA (Activin Receptor), ADAM (A Desintegrin and Metalloprotease-like Domain), ADAMTS (A Disintegrin-like and Metalloproteinase Domain with Thrombospondin Type I Motifs), ALCAM (Activated Leukocyte Cell Adhesion Molecule), ALK (Activin Receptor-like Kinase) ANG (Angiogenin), Ang (CC Chemokine Receptors), APAF-1 (Apoptosis Protease Activating Factor-1), APE (AP Endonuclease), APJ (A Seven Transmembrane-domain Receptor), APP (Amyloid Precursor Protein), APRIL (a Proliferation-inducing Ligand), AR (Amphiregulin), ARC (Agouti-related Transcript), ART (Fibroblast Growth Factor), Axl (a Receptor Tyrosine Kinase), beta2M (beta2 Microglobulin), B7-H (B7 Homolog), BACE (beta-site APP Cleaving Enzyme), Bad (Bcl-xL/Bcl-2 Associated Death Promoter), BAFF (B cell Activating Factor), Bag-1 (Bcl-2-associated Anthanogene-1), BAK (Bcl-2 Antagonist/Killer), Bax (Bcl Associated X Protein), BCA-1 (B-Cell-attracting Chemokine 1), BCAM (Basal-cell Adhesion Molecule), Bcl (B-Cell Lymphoma/Leukemia), BCMA (B Cell Maturation Factor), BDNF (Brain-derived Neurotrophic Factor), beta-ECGF (beta Endothelial Cell Growth Factor), BID (BH3 Interacting Domain Death Agonist), Bik (Bcl-2 Interacting Killer), BIM (Bcl-2 Interacting Mediator of Cell Death), BLC (B-Lymphocyte Chemoattractant), BL-CAM (B-lymphocyte Cell Adhesion Molecule), BLK (Bik-like Killer Protein), BMP (Bone Morphogenetic Protein), BMPR (Bone Morphogenetic Protein Receptor), beta-NGF (beta Nerve Growth Factor), BOK (Bcl-2-related Ovarian Killer), BPDE (Benzo(a)Pyrene-Guanosine-BSA) , BPDE-DNA (Benzo(a)Pyrene-Diol Epoxide-DNA), BTC (beta cellulin), C10 (a Novel Mouse CC Chemokine), CAD-8 (Cadherin-8), cAMP (Cyclic AMP), Caspase (Caspase-1), CCI (CC Chemokine Inhibitor), CCL (CC Chemokine Ligands), CCR (CC Chemokine Receptors), CD (Cluster of Differentiation), CD30L (CD30 Ligand), CD40L (CD40 Ligand), CFTR (Cystic Fibrosis Transmembrane Conductance Regulator), cGMP (Cyclic GMP), CINC (Cytokine-induced Neutrophil Chemotactic Factor), CKbeta8-1 (Chemokine beta 8-1), CLC (Cardiotrophin-like Cytokine), CMV UL (Cytomegalovirus ORFUL), CNTF (Ciliary Neurotrophic Factor), CNTN-1 (Contactin-1), COX (Cyclooxygenase), C-Ret (a Receptor Tyrosine Kinase), CRG-2 (a Mouse CXC Chemokine), CT-1 (Cardiotrophin 1), CTACK (Cutaneous T-cell Attracting Chemokine), CTGF (Connective Tissue Growth Factor), CTLA-4 (Cytotoxic T-lymphocyte-associated Molecule 4), CXCL (CXC Chemokine Ligands), CXCR (CXC Chemokine Receptors), DAN (Differential Screening-selected Gene Aberrant in Neuroblastoma), DCC (Deleted in Colorectal Cancer), DcR3 (Decoy Receptor 3), DC-SIGN (Dendritic Cell-specific ICAM-3-grabbing Nonintegrin), Dhh (Desert Hedgehog), DNAM-1 (DNAX Accessory Molecule 1), Dpp (Decapentaplegic), DR (Death Receptor), Dtk (Developmental Tyrosine Kinase), ECAD (E-Cadherin), EDA (Ectodysplasin-A), EDAR (Ectodysplasin Receptor), EGF (Epidermal Growth Factor), EMMPRIN (Extracellular Matrix Metalloproteinase Inducer, CD 147), ENA (Epithelial-derived Neutrophil Attractant), eNOS (Endothelial Nitric Oxide Synthase), Eot (Eotaxin Epo

Erythropoietin), ErbB3 (Erb B3 Receptor Protein Tyrosine Kinase), ERCC (Excision Repair Cross-complementing), ET-1 (Endothelin-1), Fas (Fibroblast-associated), FEN-1 (Flap Endonuclease), FGF (Fibroblast Growth Factor), FL (Fas Ligand Fas$_L$), FLIP (FLICE Inhibitory Proteins), Flt-3 (fins-like Tyrosine Kinase 3), Fractalkine, Gas 6 (Growth-arrest-specific Protein 6), GCP-2 (Granulocyte Chemotactic Protein 2), G-CSF (Granulocyte Colony Stimulating Factor), GDF (Growth Differentiation Factor), GDNF (Glial cell line-derived Growth Factor), GFAP (Glial Fibrillary Acidic Protein), GFRa-1 (Glial Cell Line-derived Neurotropic Factor Receptor a 1), GITR (Glucocorticoid Induced TNF Receptor Family Related Gene), Glut 4 (Insulin Regulated Glucose Transporter Protein), GM-CSF (Granulocyte Macrophage Growth Factor), gp130 (glycoprotein 130), GRO (Growth Related Protein a), HB-EGF (Heparin Binding Epidermal Growth Factor), HCC (Hemofiltrate CC Chemokine), HCMV UL (Human Cytomegalovirus ORFUL), HGF (Hepatocyte Growth Factor), HRG (Heregulin), Hrk (Harakiri HVEM Herpes virus Entry Mediator), I-309 (a human CC chemokine), IAP (Inhibitors of Apoptosis), ICAM (Intercellular Adhesion Molecule, ICOS (Inducible Co-stimulator), IFN (Interferon Ig Immunoglobulin), IGF (Insulin-like Growth Factor), IGFBP (Insulin-like Growth Factor Binding Protein), IL-1a (hInterleukin-1a), hIL-1b (Interleukin-1b), hIL-2(Interleukin-2), hIL-3 (Interleukin-3), hIL-4 (Interleukin-4), WL-5 (Interleukin-5), hIL-6 (Interleukin-6), hIL-7 (Interleukin-7), ML-IO (Interleukin-10). hIL-11 (Interleukin-11), hIL-12 (Interleukin-12), hIL-13 (Interleukin-13), hIL-15 (Interleukin-15), hIL-18 (Interleukin-18), iNOS (Inducible Nitric Oxide Synthase), IP-10 (Interferon gamma Inducible Protein 10), I-TAC (Interferon-inducible T-cell a Chemoattractant), JE (Mouse homologue of human MCP-1), KC (Mouse homologue of human GRO), KGF (Keratinocyte Growth Factor), LAMP (Limbic System-associated Membrane Protein), LAP (Latency-associated Peptide), LBP (Lipopolysaccharide-bin ding Protein), LDGF (Leukocyte-derived Growth Factor), LECT2 (Leukocyte Cell-Derived Chemotaxin 2), LFA-1 (Lymphocyte Function-associated Molecule-1Lfo), Lfo (Lactoferrin), LIF (Leukemia Inhibitory Factor), LIGHT (Name derived from Homologous to Lymphotoxins, Inducible expression, competes with HSV Glycoprotein D for HVEM, a receptor expressed on T-lymphocytes), LIX (LPS-induced CXC Chemokine), LKN (Leukotactin), Lptn (Lymphotactin), LT-alpha (Lymphotoxin a (aka TNF-alpha)), LT-beta (Lymphotoxin beta (aka p33)), LTB4 (Leukotriene B4), LTBP-1 (Latent TGF-beta bp1), MAG (Myelin-associated Glycoprotein), MAP2 (Microtubule-associated Protein 2), MARC (Mast Cell Activation-Related Chemokine), MCAM (Melanoma Cell Adhesion Molecule (aka MUC 18, CD 146)), MCK-2 (Mouse Cytomegalovirus Viral CC Chemokine Homolog 2), MCP (Monocyte Chemotactic Protein), M-CSF (Macrophage Colony Stimulating Factor), MDC (Macrophage-derived Chemokine (aka STP-I)), Mer (Tyrosine Protein Kinase), MGMT (O-6 Methylguanine-DNA Methyltransferase), MIF (Macrophage Migration Inhibitory Factor), MIG (Monokine Induced by IFN-g), MIP (Macrophage %%%Inflammatory%%% protein), MK (Midkine), MMACI (Mutated in Multiple Advanced Cancers Protein 1), MMP (Matrix Metalloproteinase), MPIF (Myeloid Progenitor Inhibitory Factor), Mpo (Myeloperoxidase), MSK (Mitogen- and Stress-activated Protein Kinase), MSP (Macrophage Stimulating Protein), Mug (Mismatch Uracil DNA Glycosylase), MuSK (Muscle-specific Kinase), NAIP (Neuronal Apoptosis Inhibitor Protein), NAP (Neutrophil Activation Protein), NCAD N-Cadherin (N-Cadherin Neural Cadherin), NCAM (Neural Cell Adhesion Molecule), nNOS (Neuronal Nitric Oxide Synthase), NO (Nitric Oxide), NOS (Nitric Oxide Synthase), Npn (Neuropilin), NRG-3 (Neuregulin-3), NT (Neurotrophin), NTN (Neurturin). OB (Leptin. product of the ob gene), OGG1 (8-oxoGuanine DNA Glycosylase). OPG (Osteoprotegerin), OPN (Osteopontin), OSM (Oncostatin M), PADPr (Poly (ADP-ribose) Polymer), PARC (Pulmonary and Activation-regulated Chemokine). PARP (Poly (ADP-ribose) Polymerase), PBR (Peripheral-type Benzodiazepine ReceptorInterleukin-1a (hIL-1a). Interleukin-1b (hIL-1b), Interleukin-2 (hIL-2), Interleukin-3 (hIL-3), Interleukin-4 (hIL-4), Interleukin-5 (hIL-5), Interleukin-6 (hIL-6), Interleukin-7 (hIL-7), Interleukin-10 (hIL-10), Interleukin-11 (ML-11), Interleukin-12 (hIL-12), Interleukin-13 (hIL-13), Interleukin-15 (hIL-15), Interleukin-18 (hIL-18), PBSF (Pre-B Cell Growth Stimulating Factor (aka SDF-1)Interleukin-1a (hIL-1a), Interleukin-1b (hIL-1b), Interleukin-2 (hIL-2), Interleukin-3 (hIL-3), Interleukin-4 (hIL-4), Interleukin-5 (hIL-5), Interleukin-6 (hIL-6), Interleukin-7 (hIL-7), Interleukin-10 (hIL-10), Interleukin-11 (hIL-11), Interleukin-12 (hIL-12), Interleukin-13 (hIL-13), Interleukin-15 (hIL-15), Interleukin-18 (hIL-18), PCAD (P-Cadherin Placental Cadherin), PCNA (Proliferating Cell Nuclear Antigen), PDGF (Platelet-derived Growth Factor), PDK-1(Phosphoinositide Dependent Kinase-1), PECAM (Platelet Endothelial Cell Adhesion Molecule), PF4 (Platelet Factor 4), PGE (Prostaglandin E), PGF (Prostaglandin F), PGJ2 (Prostacyclin PGJ2 Prostaglandin J2), PIN (Protein Inhibitor of Neuronal Nitric Oxide Synthase), PLA2 (Phospholipase A2), P1gF (Placenta Growth Factor), PLP (Proteolipid Protein), PP14 (Placental Protein 14), PS (Presenilin), PTEN (Protein Tyrosine Phosphatase and Tensin Homolog, see MMAC PTN Pleiotrophin), Rb1 (S. cerevisiae homolog of RAD51), RANK (Receptor Activator of NF-kappa-B), RANTES (Regulated upon activation, normal T cell Expressed and Secreted), Ret (Proto-oncogene Tyrosine-protein Kinase Receptor), RPA2 (Replication Protein A2), RSK (Ribosomal Protein S6 Kinase II), SCF/KL (Stem Cell Factor/KIT Ligand), SDF-1 (Stromal Cell-derived Factor 1 (aka PBSF)), sFRP-3 (Secreted Frizzled Related Protein), Shh (Sonic Hedgehog), SIGIRR (Single Ig Domain Containing IL-1 Receptor-related Molecule), SLAM (Signaling Lymphocytic Activation Molecule), SLPI (Secretory Leukocyte protease Inhibitor), SMAC (Second Mitochondria-derived Activator of Caspase), SMDF (Sensory and Motor Neuron-derived Factor). SOD (Superoxide Dismutase), SPARC (Secreted Protein Acidic and Rich in Cysteine). Stat (Signal Transducer and Activator of Transcription), TACE (TNF-alpha-Converting Enzyme). TACI (Transmembrane Activator and CAML Interactor). TARC (Thymus and Activation-regulated Chemokine), TCA-3 (a CC Chemokine), TECK (Thymus-expressed Chemokine), TERT (Telomerase Reverse Transcriptase), TfR (Transferrin Receptor), TGF (Transforming Growth Factor), Thymus Ck-1 (Thymus Chemokine 1). Tie (Tyrosine Kinase with immunoglobulin and Epidermal Growth Factor Homology Domains), TIMP (Tissue Inhibitors of Metalloproteinases) TIQ (N-methyl-6,7-dihydroxytetrahydroisoquinoline), Tmpo (Thymopoietin), TNF-R (TNF- Receptor), TNF (Tumor Necrosis Factor), TP-1 (Trophoblast Protein-1), Tpo (Thrombopoietin), TRAIL (TNF-related Apoptosis-inducing Ligand). TRAIL R (TRAIL Receptor), TRANCE (TNF-related Activation-induced Cytokine), TRF (Telomeric Repeat Binding Factor), Trk (Neurotrophic Tyrosine Kinase Receptor), TROP-2 (Tumor Associated Calcium Signal Transducer), TSG (Twisted Gastrulation), TSLP (Thymic Stromal Lymphopoietin). TWEAK (TNF-like and Weak Inducer of Apoptosis), TXB2 (Thromboxane B2). Ung (Uracil-N-Glycosylase), uPAR (Urokinase-type Plasminogen Activator Receptor), uPAR-1 (Urokinase-type Plasminogen Activator Receptor 1), VCAM-1 (%%%Vascular%%% Cell Adhesion Molecule 1), VECAD (VE-Cadherin %%%Vascular%%% Epithelium Cadherin), VEGF (%%%Vascular%%% Endothelial Growth Factor), VEGI (%%%Vascular%%% Endothelial Growth Inhibitor), VIM (Vimentin). VLA-4 (Very Late Antigen-4). W/F-1 (Wnt Inhibitory Factor), XIAP (X-linked Inhibitor of Apoptosis) or XPO (Xeroderma Pigmentosum D). The heterologous DNA sequence encodes a protein selected from Bc1-2. Bc1-w and Bc1-xy, Bc1-2-associated athanogene 1. CCAAT/enhancer binding protein (C/EBP), empty spiracles homolog 1 (Drosophila), empty spiracles homolog 2 (Drosophila), forkhead box G1, proprotein convertase subtilisin/kexin type 9, suppressor of cytokine signaling 2, T-cell leukemia, homeobox 1, T-cell leukemia, homeobox 3, insulin-like growth factor 1. neuregulin 1, neurotrophin 5. cut-like 1 (Drosophila), growth factor independent 1, mucolipin 3, mucosal %%%vascular%%% addressin cell adhesion molecule 1, tumor susceptibility gene 101, endothelin 3, endothelin receptor type B and/or a bone morphogenetic protein (BMP) such as BMP1, BMP2, BMP3 or %%%BMP4%%%. The artificial chromosome is a human artificial chromosome. Preferred Method. Modulating the genetic potential of a stem cell comprises introducing into the stem cell or a parent of the stem cell an artificial chromosome comprising a neocentromere having centromeric chromatin domains, which comprises expressible genetic material within the centromeric chromatin domains or in region proximal to it, which modifies or introduces at least one trait in the stem cell. Directing differentiation, proliferation or self-renewal of a stem cell comprises introducing into the stem cell or a parent of said stem cell an artificial chromosome comprising a neocentromere having centromeric chromatin domains, which comprises genetic material within the centromeric chromatin domains or in a region proximal to it, which is capable of generating an expression production which modulates stem

cell differentiation, proliferation and/or self-renewal. Altering the genetic potential of a stem cell or its daughter cell comprises incorporating into a stem cell or its parent at least one artificial chromosome comprising a neocentromere having centromeric chromatin domains of mammalian, avian or other higher eukaryote DNA origin. Differentiating a stem cell comprises introducing an artificial or engineered chromosome comprising a neocentromere having centromeric chromatin domains of mammalian, avian or plant or higher eukaryote DNA. The method alternatively comprises introducing into a stem cell a mammalian artificial or engineered chromosome comprising a neocentromere having centromeric chromatin domains of mammalian origin. Treating a subject therapeutically or prophylactically comprises administering to the subject a stem cell of Claim 1 or a stem cell generated from the method cited above. The subject is a human. ACTIVITY - Immunosuppressive. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The stem cells are useful for tissue repair, replacement, rejuvenation and/or augmentation therapy, e.g. for treating patients requiring organ transplantation. EXAMPLE - Mouse F9 teratocarcinoma cells, human HCT116, human 293T and mouse ES cell derivatives were cultured in Dulbecos Modified Eagle Medium supplemented with 10% v/v FCS, penicillin, streptomycin. Growth medium for mouse ES lines was supplemented with leukemia-inhibitory factor (LIF) and (beta-mercaptoethanol). CHO cell lines and derivative somatic cell hydrids were cultured Ham's F12 medium supplemented with 200 microg/ml zeocin. All cells were maintained at sub confluency and were split 1:4 at 24 hr prior to RNA isolation to ensure logarithmic growth of harvest.(168 pages)

2/7/26 (Item 7 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.
(c) 2008 The Thomson Corp. All rts. reserv.

0370312 DBR Accession No.: 2005-16018 PATENT
New postpartum-derived cell capable of self-renewal and expansion in culture and that can differentiate into a cell of an osteogenic or chondrogenic phenotype, for diagnosing or treating bone or cartilage disorders, e.g. rickets - cell culture medium expansion and differentiation for use in disease therapy and tissue engineering
AUTHOR: KIHM A J; SEYDA A; DHANARAJ S; WANG Z; HARMON A M; HARRIS I R; MESSINA D J; MISTRY S; YI C; GOSIEWSKA A
PATENT ASSIGNEE: ETHICON INC 2005
PATENT NUMBER: WO 2005038012 PATENT DATE: 20050428 WPI ACCESSION NO.: 2005-315703 (200532)
PRIORITY APPLIC. NO.: US 483264 APPLIC. DATE: 20030627
NATIONAL APPLIC. NO.: WO 2004US20958 APPLIC. DATE: 20040628
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A postpartum-derived cell comprising a cell derived from human postpartum tissue substantially free of blood, where the cell is capable of self-renewal and expansion in culture and has the potential to differentiate into a cell of an osteogenic or chondrogenic phenotype, where the cell requires L-valine for growth, and where the cell is capable of growth in about 5-20% oxygen, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) methods of inducing differentiation of the postpartum-derived cell to a chondrogenic or osteogenic phenotype; (2) the cell produced by (1); (3) a cell population comprising the postpartum-derived cell; (4) a cell lysate prepared from the cell population; (5) a soluble cell fraction prepared from the cell lysate; (6) an extracellular matrix of the cell population, or a matrix comprising the cell population; (7) a composition comprising the cell population and one or more bioactive factors; (8) a pharmaceutical composition comprising the cell, extracellular matrix or lysate, and a pharmaceutical carrier; (9) a cell culture comprising the cell in a culture medium; (10) methods of treating a condition in a patient, particularly a patient having a bone or cartilage condition; (11) methods of regenerating a tissue in a patient; (12) a conditioned medium generated by the growth of the culture of (9); (13) methods for identifying a compound that stimulates chondrogenesis or osteogenesis of a postpartum-derived cell, or that is toxic to the postpartum-derived cell; (14) a kit comprising at least one new cell and at least one additional component of a matrix, a hydrating agent, a cell culture substrate, a differentiation-inducing agent, and cell culture media. BIOTECHNOLOGY - Preferred Cell: The cell further comprises at least one of the following characteristics: (a) production of at least one of granulocyte chemotactic protein 2 (GCP-2), reticulon 1, tissue factor, vimentin, and alpha-smooth muscle actin; (b) lack of production of at least one of GRO-alpha or oxidized low density lipoprotein receptor, as detected by flow cytometry; (c) production of at least one of CD10, CD13, CD44, CD73, CD90, platelet derived growth factor receptor-alpha (PDGFr-alpha), programmed-death ligand 2 (PD-L2) and human leukocyte antigen (HLA)-A, B or C; (d) lack of production of at least one of CD31, CD34, CD45, CD80, CD86, CD117, CD141, CD178, B7-H2, HLA-G, and HLA-DR, DP or DQ, as detected by flow cytometry; (e) expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an iliac crest bone marrow cell, is increased for at least one of interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; and tumor necrosis factor, alpha-induced protein 3 or expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an iliac crest bone marrow cell, is reduced for at least one of: short stature homeobox 2; heat shock 27kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin; cDNA DKFZp586M2022 (from clone DKFZp586M2022); mesenchyme homeobox 2; sine oculis homeobox homolog 1; crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin; src homology 3 (SH3) and cysteine rich domain; B-cell translocation gene 1, anti-proliferative; cholesterol 25-hydroxylase; runt-related transcription factor 3; hypothetical protein FLJ23191; interleukin 11 receptor, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7; hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C; iroquois homeobox protein 5; hephaestin; integrin, beta8; synaptic vesicle glycoprotein 2; cDNA FLJ12280 fis, clone MAMMA 1001744; cytokine receptor-like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha7; DKFZP586L151 protein; transcriptional co-activator with PDZ-binding motif (TAZ); sine oculis homeobox homolog 2; KIAA1034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); cDNA clone EUROIMAGE 1966422; EphA3; KIAA0367 protein; natriuretic peptide receptor C/guanylate cyclase C (atrionatriuretic peptide receptor C); hypothetical protein FLJ14054; cDNA DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5; EGF-containing fibulin-like extracellular matrix protein 1; BCL2/adenovirus E1B 19kDa interacting protein 3-like, AE binding protein 1; cytochrome c oxidase subunit VIIa polypeptide 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; and insulin-like growth factor binding protein 2, 36kDa, (g) secretion of at least one of monocyte chemotactic protein-1, interleukin(IL)-6, IL-8, granulocyte chemotactic protein-2, hepatocyte growth factor, keratinocyte growth factor, fibroblast growth factor, heparin binding-epidermal growth factor, brain derived neurotrophic factor, thrombopoietin, macrophage %%%inflammatory%%% protein (MIP)-1a, RANTES, and tissue inhibitor of matrix metalloprotease 1; (h) lack of secretion of at least one of transforming growth factor-beta2, angiopoietin-2, platelet derived growth factor-bb, macrophage %%%inflammatory%%% protein 1beta (MIPlb), I309, macrophage-derived chemokine, and %%%vascular%%% endothelial growth factor, as detected by ELISA; and (i) the ability to undergo at least 40 population doublings in culture. The cell has been isolated from a post-partum placenta or its fragment by

enzymatic dissociation with at least one of a matrix metalloprotease, a neutral protease, and a mucolytic enzyme that digests hyaluronic acid. Preferred Method: Inducing differentiation of the postpartum-derived cell to a chondrogenic phenotype comprises exposing the cell to one or more chondrogenic differentiation-inducing agents. The chondrogenic differentiation-inducing agent comprises at least one of transforming growth factor-beta3 (TGFbeta3) and growth and differentiation factor-5 (GDF-5). The method further comprises culturing the cell in chondrogenic medium, which comprises Dulbecco's modified Eagle's medium, L-glutamine, sodium pyruvate, L-proline, dexamethasone, L-ascorbic acid, insulin, transferrin, selenium, and an antibiotic agent. The chondrogenic medium further comprises at least one of collagen and sodium hydroxide. The method further comprises evaluating differentiation of the cell by a pellet culture assay or by detecting the presence of a glycosaminoglycan or collagen. The step of evaluating comprises staining the cell with Safranin-O or hematoxylin/eosin. Inducing the differentiation of the above postpartum-derived cell to an osteogenic phenotype comprises exposing the cell to one or more osteogenic differentiation-inducing agents. The differentiation-inducing agent comprises at least one of bone morphogenic protein (BMP)-2, BMP-4, and transforming growth factor-beta1. The method further comprises culturing the cell in osteogenic medium comprising Dulbecco's modified Eagle's medium-low glucose, serum, beta-glycerophosphate, dexamethasone, ascorbic phosphate salt, and at least one antibiotic or antimycotic agent. The method further comprises evaluating the differentiation by detecting an osteogenic lineage-specific marker. The marker is osteocalcin, bone sialoprotein, or alkaline phosphatase. It further comprises detecting the differentiation by measuring mineralization. The step of detecting comprises von Kossa staining. Treating a condition in a patient comprises administering to the patient one or more postpartum-derived cells mentioned above. The condition is a bone or cartilage condition, such as a congenital bone or cartilage defect, meniscal injury or defect, bone/spinal deformation, osteosarcoma, myeloma, bone dysplasia or scoliosis, osteoporosis, periodontal disease, dental bone loss, osteomalacia, rickets, fibrous osteitis, renal bone dystrophy, spinal fusion, spinal disc reconstruction or removal, Paget's disease of bone, rheumatoid arthritis, osteoarthritis, or a traumatic or surgical injury. The postpartum-derived cells are administered with at least one other cell type, such as bone marrow cells, chondrocytes, chondroblasts, chondrocyte progenitor cells, osteocytes, osteoblasts, osteoclasts, bone lining cells, stem cells, or other pluripotent or multipotent cell. The postpartum-derived cells are inoculated on a matrix that is implanted into the patient. The postpartum-derived cells are induced to differentiate to a chondrogenic or osteogenic phenotype prior to the step of administering. These cells are co-administered with at least one bioactive factor. The cells are administered to a bone or a cartilage of the patient. Alternatively, treating a patient having a bone or cartilage condition comprises administering to the patient the extracellular matrix of the cell cited above, or the cell lysate or conditioned medium as mentioned above. Regenerating a tissue in a patient comprises administering the cell population cited above to the patient. The tissue is bone or cartilage. The cells are implanted into the patient. Identifying a compound that stimulates chondrogenesis or osteogenesis of a postpartum-derived cell comprises contacting the cell cited above with the compound and monitoring the cell for a marker of chondrogenesis or osteogenesis. Identifying a compound that is toxic to the above postpartum-derived cell comprises contacting the cell with the compound and monitoring survival of the cell. Preferred Cell Population: The cell population is substantially homogeneous or heterogeneous. It further comprises at least one cell type of bone marrow cells, chondrocytes, chondroblasts, chondrocyte progenitor cells, stem cells, or other pluripotent or multipotent cell. Preferred Composition: The bioactive factor is a chondrogenic or an osteogenic differentiation-inducing factor. The pharmaceutical composition comprises an amount of the cells, extracellular matrix or lysate to treat a bone or cartilage condition. The pharmaceutical composition further comprises at least one other cell type of stem cells, bone marrow cells, chondrocytes, chondroblasts, osteocytes, osteoblasts, osteoclasts, bone lining cells, and other bone or cartilage progenitor cells. Preferred Cell Culture: The culture medium comprises chondrogenic medium or osteogenic medium. The cell culture further comprises at least one chondrogenic differentiation-inducing agent. The chondrogenic differentiation-inducing agent is at least one of transforming growth factor-beta1 or growth and differentiation factor-5. It further comprises at least one osteogenic differentiation-inducing agent, such as transforming growth factor-beta1, BMP2 or %%%BMP4%%%. Preferred Matrix: The matrix comprises a 3-dimensional scaffold. Preferred Kit: The matrix is a 3-dimensional scaffold and the cell is seeded on the scaffold. The differentiation-inducing agent is an osteogenic differentiation-inducing agent or a chondrogenic differentiation-inducing agent. ACTIVITY - Osteopathic; Cytostatic; Antiarthritic; Antirheumatic; Vulnerary. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The composition and methods are useful for diagnosing or treating bone or cartilage disorders, such as a congenital bone or cartilage defect, meniscal injury or defect, bone/spinal deformation, osteosarcoma, myeloma, bone dysplasia or scoliosis, osteoporosis, periodontal disease, dental bone loss, osteomalacia, rickets, fibrous osteitis, renal bone dystrophy, spinal fusion, spinal disc reconstruction or removal, Paget's disease of bone, rheumatoid arthritis, osteoarthritis, or a traumatic or surgical injury. These may also be used in research applications or in screening for agents that may treat the disorders (claimed). ADMINISTRATION - Administration can be intramuscular, ophthalmic, intraarterial, intravenous, subcutaneous, oral, nasal, intraperitoneal, and the like. No dosage given. EXAMPLE - No relevant example given. (146 pages)

2/7/27 (Item 8 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.
(c) 2008 The Thomson Corp. All rts. reserv.

0316052 DBR Accession No.: 2003-17192 PATENT
Transferring nucleic acid into cells associated with fluid space by contacting wound site situated in tissue associated with fluid space, with composition comprising nucleic acid and biocompatible matrix - gene transfer expression in cell for use in disease therapy and gene therapy
AUTHOR: SOSNOWSKI B A; PIERCE G
PATENT ASSIGNEE: SELECTIVE GENETICS INC 2003
PATENT NUMBER: WO 200329429 PATENT DATE: 20030410 WPI ACCESSION NO.: 2003-436202 (200340)
PRIORITY APPLIC. NO.: US 327513 APPLIC. DATE: 20011003
NATIONAL APPLIC. NO.: WO 2002US31546 APPLIC. DATE: 20021002
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Transferring (M1) a nucleic acid molecule into cells associated with a fluid space, involves contacting a wound site with a composition (I) comprising a nucleic acid molecule and a biocompatible matrix, the wound site being situated in a tissue associated with the fluid space. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) stimulating (M2) gene expression in cartilage progenitor cells located within a cartilage progenitor tissue site of an animal, involves contacting the tissue site with a composition comprising a chondrogenic gene and a biocompatible matrix; (2) stimulating (M3) cartilage repair or regeneration, by implanting at a cartilage defective site a matrix-gene composition comprising a chondrogenic gene and a biocompatible matrix; (3) treating (M4) arthritis, by implanting at a cartilage defective site a matrix- gene composition comprising chondrogenic gene and a biocompatible matrix; (4) treating (M5) ischemic heart disease by implanting a matrix-gene composition comprising an angiogenic gene and a biocompatible matrix into an ischemic region; and (5) a composition comprising multiple genes associated with a multi-partitional biocompatible matrix. BIOTECHNOLOGY - Preferred Method: The wound site is situated in a tissue e.g., cartilage, cardiac muscle or bone/cartilage interface, associated with the fluid space. The method involves contacting (I) with a wound site which is a wound induced by injury or a disease state, or an iatrogenic wound. The contacting process involves bringing the nucleic acid molecule into contact with the biocompatible matrix to

form a matrix-nucleic acid composition and bringing the matrix-nucleic acid composition into contact with the tissue site. The nucleic acid molecule is a DNA molecule complexed with anti-DNA antibodies, histone H1, a polycation or is a DNA molecule comprising a promoter operably linked to a sequence encoding a gene product. The DNA molecule encodes a therapeutic protein such as a growth factor chosen from transforming growth factor (TGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), hepatocyte growth factor (HGF), epidermal growth factor (EGF), connective tissue growth factor (CTGF), bone morphogenic factor (BMP) or a cartilage-derived morphogenic protein (CDMP). Optionally, the therapeutic protein is a growth hormone or human parathyroid hormone (PTH). The therapeutic protein may be latent TGF-beta binding protein (LTBP), keratinocyte growth factor (KGF), %%%vascular%%% endothelial growth factor (VEGF), Factor VIII, Factor IX, erythropoietin (EPO), tissue plasminogen activator (TPA), leukemia inhibitory factor (LIF), parathyroid hormone-related peptide (PTHrP), activin, inhibin, interleukin, macrophage-colony stimulating factor (M-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), skeletal growth factor (SGF), chondromodulin, mono or polyclonal antibodies and its fragments, enzymes involved in production and/or processing of collagen, enzymes involved in production and/or processing of hyaluronic acid, transcription factors that trigger proliferation, differentiation, and morphogenic pathways, cell survival factors, or cell death factors. Optionally, the nucleic acid molecule is an RNA molecule, antisense nucleic acid molecule, a linear nucleic acid molecule, a plasmid or a recombinant insert within the genome of a recombinant virus. The biocompatible matrix is a biological matrix which comprises a polymer, and is chosen from collagen, purified proteins, purified peptides, polysaccharides (e.g. chitosan, alginate, dextran, hyaluronic acid and cellulose), and extracellular matrix compositions. Preferably, the biological matrix comprises type I collagen, type II collagen, mineralized collagen or atelocollagen collagen. Optionally, the biocompatible matrix is a synthetic matrix which comprises a polymer chosen from polyethylene glycols or their derivatives, polyesters, polyethers, polyanhydrides, polyalkyloyanoacrylates, polyacrylamides, polyorthoesters, polyphospazenes, polyvinylacetates, block copolymers, polytetrafluoroethylene (PTFE), and polyurethanes. Optionally, the polymer comprises lactic acid or glycolic acid, or may be a copolymer which comprises lactic acid and glycolic acid (PLGA). The biocompatible matrix is biodegradable or non-biodegradable. The non- biodegradable matrix comprises a polymer such as poly(dimethysiloxane) or poly(ethylene-vinyl acetate). The biocompatible matrix is a collagen, metal, hydroxyapatite, bioglass, aluminate, bioceramic materials, hyaluronic acid polymers, acrylic ester polymer, lactic acid polymer, glycolic acid polymer, lactic acid/glycolic acid polymer, purified proteins, purified peptides, and extracellular matrix compositions. Preferred Method: In (M2), the contacting process involves bringing the chondrogenic gene with the biocompatible matrix to form a matrix-gene composition and bringing the matrix-gene composition into contact with the tissue site. The biocompatible matrix is a collagen preparation, hydroxyapatite matrix, a lactic acid polymer matrix or a fibrin matrix. In (M3), the matrix comprises a first portion and a second portion. The first portion comprises a gene to stimulate cartilage growth and the second portion comprises a gene to stimulate bone growth. ACTIVITY - Vulnerary; Antiarthritic; Antiinflammatory; Vasotropic. MECHANISM OF ACTION - Gene therapy. Influence of collagen-immobilized fibroblast growth factor (FGF) genes on muscle wound repair was examined using the rodent hind limb model. At day 14 following delivery of DNA/FGF2) formulated in a blend of 1% collagen and 1% gelatin, trichrome stains revealed that these matrices were well infiltrated by both mononuclear cells and elongated fibroblastoid cells. Many of these cells were organized around simple single-walled vessel, and may represent %%%vascular%%% precursors giving rise to neovasculature. The presence of erythrocytes with vessel lumens confirmed that these vessels were perfused. By day 21 post-treatment, in addition to microvasculature, well-organized muscular arterioles were also present. Skeletal muscle bundles were scattered throughout the collagen-gelatin matrix, which appeared to be reduced in volume over that seen at day 14. neither the residual matrix nor the surrounding tissue showed any signs of edema.

Very similar observations were seen following the delivery of collagen-gelatin-DNA(FGF6) to muscle wounds, including the development of both micro- and macrovasculature. Delivery of the control transgene luciferase induced a much different response. Even at day 21, considerable collagen-gelatin matrix remained, and although a mononuclear cell infiltrate was present, blood- perfused vessels perfused were rare. infiltrating cells were organized into discrete areas, however the majority of these structures were not true vasculature in that they were not lined by a continuous endothelium and were not perfused with blood. Finally, delivery of FGF2 protein was seen to induce a limited angiogenic response comprised of small capillaries. Arteriogenesis similar to that induced by FGF2 or FGF6 gene delivery was not observed. USE - (M1) is useful for transferring a nucleic acid molecule into cells associated with a fluid space. (M2) is useful for stimulating gene expression in cartilage progenitor cells located within a cartilage progenitor tissue site of an animal, where expression of the gene in the cell stimulates the cells to promote cartilage tissue repair or regeneration. The cartilage progenitor tissue site of an animal is a site of cartilage injury (a partial-thickness injury or a full-thickness injury), or is a cartilage cavity site, or is the result of surgery or the removal of cartilage tumor. The chondrogenic gene is in the form of plasmid DNA, a DNA insert within the genome of a recombinant adenovirus, a DNA insert within the genome of a recombinant adeno-associated virus (AAV) or a DNA insert within the genome of a recombinant retrovirus. The chondrogenic gene is parathyroid hormone (PTH) gene, bone morphogenic factor (BMP) gene, a cartilage-derived morphogenic protein (CDMP) gene, a growth factor gene, a growth factor receptor gene (e.g. IGF receptor gene or MBP receptor gene), where the growth factor gene is fibroblast growth factor (FGF) gene, insulin-like growth factor (IGF) gene, hepatocyte growth factor (HGF) gene, a gene in the transforming growth factor (TGF) family of genes, epidermal growth factor (EGF) gene, connective tissue growth factor (CTGF) gene, leukemia inhibitory factor (LIF) gene, parathyroid hormone-related peptide (PTHrP) gene, platelet-derived growth factor (PDGF) gene, skeletal growth factor (SGF) gene, BIP gene, MP52 gene, chondromodulin gene, preferably basic FGF gene, IGF-I or IGF-II gene, TGFalpha, TGFbeta1 or TGFbeta2, BMP2, BMP3, %%%BMP4%%%, BMP5, BMP6, BMP7, BMP8, BMP9, BMP10, BMP11, BMP12 or BMP13 gene. (M3) is useful for stimulating cartilage repair or regeneration. (M4) is useful for treating arthritis, where the chondrogenic gene that is implanted is an IL-4 gene, or a gene that encodes either a ribozyme that cleaves mRNAs for an %%%inflammation%%% mediator, or an antisense nucleic acid that binds to mRNA for an %%%inflammation%%% mediator such as IL-1, IL-6, TNF-alpha, granulocyte-macrophage colony stimulating factor (GM-CSF), a soluble receptor that binds to a mediator of %%%inflammation%%%, or an antibody or its fragment that binds to a mediator of %%%inflammation%%%. (M5) is useful for treating ischemic heart disease, where the angiogenic gene that is implanted is FGF gene, VEGF gene, TNF-alpha gene, HGF gene, or a PDGF gene (all claimed). ADMINISTRATION - The gene-matrix composition is transferred directly to the site of a naturally occurring wound or an iatrogenic injury or the matrices may be surgically placed in a wound made in an organ. The matrices may also be implanted via grafting, injection, catheterization, laproscopic surgical procedures, or arthroscopic surgery. ADVANTAGE - Direct plasmid DNA transfer from a matrix to a mammalian repair cell, through stimulation of the wound healing process, has the following advantages: (a) each are capable of producing and purifying DNA constructs; (b) matrices can act as structural scaffolds that, in and of themselves, promote cell in growth and proliferation, thus facilitating the targeting of repair cells to gene transfer; (c) the introduction of a biocompatible matrix to tissues associated with a fluid space results in less damage to surrounding tissues during introduction; (d) the biocompatible matrix may be implanted through or across the fluid space without harming other tissue; (e) the method therefore, is a minimally invasive means of utilizing gene therapy to introduce therapeutic molecules to tissues associated with fluid spaces; (f) the proximity of a fluid space facilitates the migration of repair cells to the biocompatible matrix that is inserted into a tissue associated with a fluid space; and (g) the methods are efficient in introducing gene therapy products to

target cells associated with a fluid space.(95 pages)

2/7/28 (Item 9 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.
(c) 2008 The Thomson Corp. All rts. reserv.

0306427 DBR Accession No.: 2003-08212 PATENT
Regulating LRP5, LRP6 or HBM activity in a subject, useful for modulating lipid levels and/or bone mass, and for in treating bone mass disorders, e.g. osteoporosis, comprises administering a composition which modulates a Dkk activity - aptamer, antisense and reporter molecular for disease diagnosis and therapy
AUTHOR: ALLEN K; ANISOWICZ A; BHAT B M; DAMAGNEZ V; ROBINSON J A; YAWORSKY P J
PATENT ASSIGNEE: GENOME THERAPEUTICS CORP; WYETH 2002
PATENT NUMBER: WO 200292015 PATENT DATE: 20021121 WPI ACCESSION NO.: 2003-129219 (200312)
PRIORITY APPLIC. NO.: US 361293 APPLIC. DATE: 20020304
NATIONAL APPLIC. NO.: WO 2002US15982 APPLIC. DATE: 20020517
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Regulating LRP5, LRP6 or HBM activity in a subject comprising administering a composition which modulates a Dkk activity, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) regulating Dkk-Wnt pathway activity in a subject; (2) modulating bone mass in a subject; (3) modulating lipid levels in a subject; (4) diagnosing low or high bone mass and/or high or low lipid levels in a subject; (5) screening for a compound which modulates the interaction of Dkk with LRP5, LRP6, HBM or a Dkk-binding fragment of LRP5, LRP6 or HBM; (6) screening a compound which modulates the interaction of Dkk with a Dkk interacting protein; (7) a composition comprising an LRP5, LRP6 or HBM activity-modulating compound, and a pharmaceutical carrier; (8) a pharmaceutical composition a compound which modulate Dkk and LRP5/LRP6/HBM interactions; (9) identifying binding partners for a Dkk protein or compounds which modulate Dkk and/or LRP5/LRP6/HBM interactions; (10) a nucleic acid encoding a Dkk interacting protein peptide aptamer comprising a nucleic acid encoding a scaffold protein in-frame with the activation domain of Gal4 or Lex A that is in frame with a nucleic acid that encodes a Dkk interacting protein amino acid sequence; (11) a vector comprising the nucleic acid of (10); (12) detecting a modulatory activity of a compound on the binding interaction of a first peptide and a second peptide of a peptide-binding pair that binds through extracellular interaction in their natural environment; (13) a transgenic animal where Dkk-1 is knocked out in a tissue-specific fashion; (14) identifying potential compounds which modulate Dkk activity; (15) a peptide aptamer comprising one of 22 13-32 residue amino acid sequences, given in the specification; (16) an antibody or antibody fragment which recognizes and binds to one or more of 18 13-17 residue amino acid sequences, given in the specification; (17) identifying Dkk interacting proteins which modulate the interaction of Dkk with the Wnt signaling pathway; (18) identifying compounds which modulate Dkk and LRP5/LRP6/HBM interactions; (19) identifying compounds which modulate the interaction of Dkk with the Wnt signaling pathway; (20) testing compounds that modulate Dkk-mediated activity in a mammal; (21) screening for compounds or compositions which modulate the interaction of Dkk and a Dkk interacting protein; and (22) an antibody or antibody fragment which recognizes and binds to a sequence selected from 18 peptide sequences given in the specification. BIOTECHNOLOGY - Preferred Method: Dkk is Dkk-1, and Dkk activity is inhibited. The Dkk activity modulates bone mass and/or lipid levels, where bone mass is increased and/or lipid levels are decreased. Increase in bone mass is determined by a decrease in fracture rate, or by an increase in bone strength, bone density, trabecular connectivity, trabecular density, cortical density, bone diameter or inorganic bone content. The composition comprises one or more compounds selected from Dkk interacting proteins or its Dkk-binding fragment. The composition comprises an antisense, siRNA, or shRNA molecule which recognizes and binds to a nucleic acid encoding one or more Dkk interacting proteins. The composition may also comprise a mimetic of a Dkk peptide aptamer, a mimetic of a Dkk interacting protein peptide aptamer, a mimetic of a Dkk interacting protein peptide aptamer, or an LRP5 peptide aptamer. The composition inhibits or enhances Dkk binding to LRP5, LRP6 or HBM, or may also inhibit or enhance Dkk interacting protein or Dkk-binding fragment binding to Dkk. The peptide aptamer OST262 comprises a 154 residue amino acid sequence, given in the specification. The composition may alternatively comprise an LRP5 antibody or its immunologically active fragment. The subject is a vertebrate or an invertebrate, preferably a mammal selected from a canine, feline, ovine, primate, equine, porcine, caprine, camelid, avian, bovine and rodent, where the primate is preferably a human. Regulating Dkk-Wnt pathway activity in a subject comprises administering a composition which modulates Dkk activity, where Wnt is selected from Wnt1-Wnt19, preferably Wnt1, Wnt3, Wnt3a or Wnt10b. The composition which modulates Dkk activity or Dkk interaction with LRP5/LRP6/HBM is administered to modulate Wnt signaling. Modulating bone mass or lipid levels in a subject comprises administering a composition which modulates Dkk activity or Dkk interaction with LRP5, LRP6 or HBM, where bone mass is increased. Increase in bone mass is determined by a decrease in fracture rate, or by an increase in bone strength, bone density, bone mineral density, trabecular connectivity, trabecular density, cortical density, bone diameter or inorganic bone content. The subject has a bone mass disorder such as bone development disorder, bone fracture, age-related loss of bone, chrondrodystrophy, drug-induced bond disorder, high bone turnover, hypercalcemia, hyperostosis, osteogenesis imperfecta, osteomalacia, osteomyelitis, osteoporosis, Paget's disease, osteoarthritis, or rickets. The composition is administered to modulate the amount of trabecular and/or cortical tissue. The lipid-modulated disorder is a cardiac condition, %%%atherosclerosis%%%, familial lipoprotein lipase deficiency, familial apoprotein CII deficiency, familial hypertriglyceridemia, multiple lipoprotein-type hyperlipidemia , elevated lipid levels due to dialysis and/or diabetes, or elevated lipid levels of unknown etiology. Diagnosing low or high bone mass and/or high or low lipid levels in a subject comprises examining expression of Dkk, LRP5, LRP6, HBM and/or HBM-like variant in the subject, and determining whether these are over- or under-expressed. Screening for a compound which modulates the interaction of Dkk with LRP5, LRP6, HBM or a Dkk-binding fragment of LRP5, LRP6 or HBM, comprises exposing Dkk and an LRP5, LRP6 and/or HBM binding fragment to a compound, and determining whether the compound modulates Dkk interaction with the LRP5, LRP6 and/or HBM binding fragment, where modulation is determine by determining if the compound binds to Dkk or the LRP5, LRP6 and/or HBM binding fragment. The Dkk or an LRP-binding fragment is attached to a substrate. The compound comprises one or more Dkk interacting proteins or Dkk binding fragment, a Dkk peptide aptamer, a mimetic of a Dkk peptide aptamer, a Dkk interacting protein peptide aptamer, an LRP5 peptide aptamer, an LRP6 antibody, or a mimetic of a Dkk interacting protein peptide aptamer. Screening a compound which modulates the interaction of Dkk with a Dkk interacting protein comprises exposing a Dkk interacting protein or a Dkk-binding fragment to a compound, determining whether the compound binds to the Dkk interacting protein or Dkk-binding fragment, and further determining whether the compound modulates the interaction of Dkk interacting protein and Dkk. Identifying compounds, which modulate Dkk and/or LRP5/LRP6/HBM interactions, comprises creating an LRP5, LRP6 or HBM fluorescent fusion protein using a fluorescent tag, creating a Dkk fusion protein comprising a second fluorescent tag, adding a test compound, and assessing changes in the ratio of fluorescent tag emissions using fluorescence Resonance energy transfer (FRET) or bioluminescence resonance Energy Transfer (BRET) to determine whether the compound modulates Dkk and LRP5/LRP6/HBM interactions. The method may alternatively comprise immobilizing LRP5/LRP6/HBM to a solid surface, treating the solid surface with a secreted Dkk protein or epitope-tagged Dkk and a test compound, and determining whether the compound regulates binding between Dkk and LRP5/LRP6/HBM using antibodies to Dkk or the epitope tag, or by directly measuring the activity of an epitope tag. The epitope tag is alkaline phosphatase, histidine, or a V5 tag. Identifying binding partners for a Dkk protein comprises exposing the Dkk protein or LRP5/LRP6 binding fragment to a potential binding partner, and determining if the potential binding

partner binds to a Dkk protein or the LRP5/LRP6 binding fragment. Detecting a modulatory activity of a compound on the binding interaction of a first peptide and a second peptide of a peptide-binding pair that binds through extracellular interaction in their natural environment, comprises: (a) culturing at least one eukaryotic cell comprising a nucleotide sequence encoding a first heterologous fusion protein comprising the first peptide or its segment joined to a transcriptional activation protein DNA binding domain, a nucleotide sequence encoding a second heterologous fusion protein comprising a second peptide or its segment joined to a transcriptional activation protein transcriptional activation domain, where binding of the first and second peptides reconstitutes a transcriptional activation protein, and a reporter element activated under positive transcriptional control of the reconstituted transcriptional activation protein, where expression of the reporter element produces a selected phenotype; (b) incubating the eukaryotic cell in the presence of a compound to detect the selected phenotype; and (c) detecting the ability of the compound to affect the binding interaction of the peptide binding pair by determining if the compound affects the expression of the reporter element which produces the selected phenotype. The first peptide is a Dkk peptide, and the second peptide is LRP5, HBMI, LRP6 or Dkk-binding portion of LRP5/LRP6/HBMI. Alternatively, the first peptide is a Dkk interacting protein or Dkk-binding fragment, and the second peptide is a Dkk peptide. The eukaryotic cell is a yeast cell such as Saccharomyces, preferably Saccharomyces cerevisiae. The Dkk is Dkk-1, and the compound comprises one or more Dkk interacting proteins or a Dkk-binding fragment. The compound is directly added to the assay or is recombinantly expressed by the eukaryotic cell in addition to the first and second peptides. The eukaryotic cell further comprises at least one endogenous nucleotide sequence encoding the DNA binding domain of a transcriptional activation protein, the transcriptional activation domain of a transcriptional activation protein or the reporter element, where at least one of the endogenous nucleotide sequences is inactivated by mutation or deletion. The peptide binding pair comprises a ligand and a receptor to which the ligand binds. The transcriptional activation protein is Gal4, Gnc4, Hap1, Adr1, Swi5, Ste12, Mcm1, Yap1, Ace1, Ppr1, Arg81, Lac9, Qa1F, VP16 or a mammalian nuclear receptor. Preferably at least one of the heterologous fusion proteins is expressed from an autonomously-replicating plasmid. The DNA binding domain is a heterologous DNA-binding domain of a transcriptional activation protein, and the DNA binding protein is a mammalian steroid receptor or bacterial LexA protein. The reporter element is a LacZ, a polynucleotide encoding luciferase, a polynucleotide encoding green fluorescent protein, or a polynucleotide encoding chloramphenicol acetyltransferase, preferably LacZ. The test sample comprises an LRP5 peptide aptamer, preferably OST262, or an LRP5 antibody. Identifying potential compounds which modulate Dkk activity comprises measuring the effect on binding of one or more Dkk interacting proteins or a Dkk-binding fragment, with a Dkk or its fragment in the presence or absence of a compound, and identifying as a potential Dkk modulatory compound a compound which modulates the binding between one or more Dkk interacting proteins or Dkk-binding fragment, and Dkk or its fragment. Identifying Dkk interacting proteins, which modulate the interaction of Dkk with the Wnt signaling pathway, comprises injecting Dkk and potential Dkk interacting protein mRNA into a Xenopus blastomere, assessing axis duplication or marker gene expression, and identifying compositions which elicit changes in axis duplication or marker gene expression as Dkk interacting proteins which modulate the interaction of Dkk with the Wnt signaling pathway. The mRNA of HBMI, LRP5/6, any wnt, Wnt antagonist, Wnt pathway modulator, or a combination of these is co-injected into the Xenopus blastomere. The marker gene analyzed is Siamois, Xnr3, slug, Xbra, HNK-1, endodermin, Xlhbox8, BMP2, %%%BMP4%%%, XLRP6, EF-1 or ODC. The method alternatively comprises transfecting cells with constructs containing Dkk and potential Dkk interacting proteins, assessing changes in expression of a reporter gene linked to a Wnt-responsive promoter, and identifying as a Dkk interacting protein in any protein which alters reporter gene expression compared with cells transfected with a Dkk construct alone. The cells are HOB-03-CE6, HKE293 or U2OS cells. The Wnt-responsive promoter is TCF or LEF. The cells are co-transfected with cytomegalovirus (CMV) beta-galactosidase. Identifying compounds which modulate the interaction of Dkk with the Wnt signaling pathway comprises transfecting cells with constructs containing Dkk and Wnt proteins, assessing changes in expression of a reporter element linked to a Wnt-responsive promoter, and identifying as Dkk/Wnt interaction modulating compound any compound which alters reporter gene expression compared to cells transfected with a Dkk construct alone. Wnt3a and Wnt1 constructs are co-transfected into the cells, where the cells are HOB-03-CE6, HKE293 or U2OS cells. The reporter element is TCF-luciferase and/or tk-Renilla. Testing compounds that modulate Dkk-mediated activity in a mammal comprises providing a group of transgenic animals having a regulatable one or more Dkk genes, a knock-out of Dkk genes or a knock in of one or more Dkk genes, providing a second group of control animals respectively for the group of transgenic animals, exposing the animals to a potential Dkk-modulating compound which modulates bone mass or lipid levels, and comparing the transgenic animals and the control group of animals and determining the effect of the compound on bone mass or lipid levels in the transgenic animals compared to the control animals. Screening for compounds or compositions which modulate the interaction of Dkk and a Dkk interacting protein comprises exposing a Dkk interacting proteins or a Dkk-binding fragment to a compound, and determining whether the compound binds to a Dkk interacting proteins or Dkk-binding fragment. Modulation is determined if the compound binds to the Dkk interacting protein or the Dkk binding fragment. Preferred Composition: The composition of (7) comprises an LRP5, LRP6 or HBM activity-modulating compound that binds to Dkk thus modulating the interaction of Dkk with LRP5, LRP6 or HBMI. The LRP5-, LRP6- or HBM-modulating compound comprises one or more Dkk interacting proteins and Dkk-binding fragments, a monoclonal antibody or its immunologically active fragment that binds to a Dkk interacting protein or Dkk binding fragment, an antisense, a siRNA or shRNA molecule that recognizes and binds to a nucleic acid encoding one or more Dkk interacting proteins, a Dkk peptide aptamer, a Dkk interacting protein peptide aptamer or its mimetic, an LRP5 peptide aptamer, preferably OST262, or an LRP5 antibody. ACTIVITY - Osteopathic; Antiinflammatory; Antiarthritic. No biological data is given. MECHANISM OF ACTION - Dkk modulator. USE - The method is useful for modulating lipid levels and/or bone mass, and is useful in treating or diagnosing abnormal lipid levels and bone mass disorders, such as osteoporosis, bond fracture, age-related loss of bone, a chondrodystrophy, drug-induced bone disorder, high bone turnover, hypercalcemia, hyperostosis, osteogenesis, imperfecta, osteomalacia, osteomyelitis, Paget's disease, osteoarthritis, and rickets. Modulators of Dkk activity are useful for as reagents in studying bone mass and lipid level modulation, in modulating Wnt signaling, or treating Dkk-mediated disorders. ADMINISTRATION - Dosage is 0.0001-50, preferably 0.1-1 mg/kg. Administration can be parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal. EXAMPLE - No relevant examples are given. (173 pages)